Masterproef
Advanced radiological techniques regarding spinal fusion

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Leen Wijnen
Scriptie ingediend tot het behalen van de graad van master in de biomedische wetenschappen
2014•2015
FACULTEIT GENEESKUNDE EN LEVENSWETENSCHAPPEN
master in de biomedische wetenschappen

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Acknowledgements

This paper represents the end of my bachelor and master course in biomedical sciences at Hasselt University. These 5 years went by so fast. I want to thank all the people of Hasselt University for the teaching during these years.

My senior internship at Ziekenhuis Oost-Limburg (ZOL) during the past 8 months was a great experience. This paper would not have been realized without the help and support of several people. Therefore I would like to take this opportunity to express my gratitude towards them. First of all, I especially thank my promotor, Prof. Dr. Vandevenne, for giving me the opportunity to perform this internship at the department of radiology, for making time to guide me, to answer my questions, to support me in writing articles and this report, to introduce me to product managers of different companies and to give me the opportunity to attend the annual meeting of the BSN (Belgium Society of Neurosurgery) at Antwerp.

I also owe my gratitude to Ellen Gielen and Leentje Dreesen for their guidance during this internship. I express my thanks to all the radiologists, assistants and all other staff members for giving answers to my questions and for making the plain films and scans. Moreover, I thank Dr. Peuskens, Dr. Buelens and the other neurosurgeons for their contribution.

I am also grateful to dr. Vanmierlo and Prof. dr. Vandersteen for their interest and listening during this research and their helpful recommendations and advice for this report.

Lastly, I deeply thank my parents, family, friends and fellow students for their support and encouragement during these 5 years and for being there for me.
List of abbreviations

ACIF  Anterior Cervical Interbody Fusion
ALARA  As Low As Reasonably Achievable
ALIF  Anterior Lumbar Interbody Fusion
AS  Ankylosing Spondylitis
ASAS  Assessment of SpondyloArthritis international Society
BASDAI  Bath Ankylosing Spondylitis Disease Activity Index
BSN  Belgian Society of Neurosurgery
CBCT  Cone-beam Computed Tomography
CRP  C-Reactive Protein
CT  Computed Tomography
CTDI  Computed Tomography Dose Index
ESNR  European Society of NeuroRadiology
FDA  Food and Drug Administration
HLA  Human Leukocyte Antigen
LBP  Low Back Pain
MCS  Mental Component Score
MRI  Magnetic Resonance Imaging
MSCT  Multi-Slice Computed Tomography
NDI  Neck-Disability-Index
NRS  Numeric-Rating-Scale
NSAIDs  Non-Steroidal Anti-Inflammatory Drugs
ODI  Oswestry-Disability-Index
PCS  Physical Component Score
PEEK  Poly-Ether Ether Ketone
PLIF  Posterior Lumbar Interbody Fusion
PMBD  Painful Monosegmental Black Disc
SF  Short Form
SIJ  SacroIliac Joint
SpA  SpondyloArthritis
STIR  Short Tau Inversion Recovery
TLIF  Transforaminal Lumbar Interbody Fusion
TNF  Tumor Necrosis Factor
TSC  Titaniuim Sputtered Coating
VAS  Visual-Analogue-Scale
XLIF  eXtreme Lateral Interbody Fusion
Summary

Introduction: Medical imaging is typically used to diagnose disease, to follow-up treatment, or to guide interventions. Bony fusion between 2 vertebrae in adults is usually acquired through disease or surgery. The general study aim is to evaluate the role of advanced imaging techniques regarding intervertebral fusion. Three particular clinical situations were chosen to challenge medical imaging regarding early diagnosis of a disease leading to intervertebral fusion, regarding follow-up of surgical intervertebral fusion and regarding image-guided intervention to postpone surgical fusion.

Subjects and methods:
- Clinical situation 1: Early diagnosis of morbus Bechterew (SpA) is of major importance to initiate adequate treatment in a timely fashion, and MRI of the axial skeleton is one of the key parameters for early diagnosis. Is MRI of the sacroiliac joints (SIJ) or MRI of both the SIJ and the spine needed for early diagnosis of morbus Bechterew? 32 MRI exams were scored by 2 independent readers according to the ASAS criteria. Cohen’s kappa was calculated and data analysis was performed using McNemar’s test.
- Clinical situation 2: For the follow-up of surgical intervertebral fusions such as ACIF, plain films and CT are generally used to define a successful radiological fusion or arthrodesis. In a pilot study, cone-beam CT (CBCT) was used for the follow-up of 1 patient over three months with detailed description of the bony fusion process.
- Clinical situation 3: Image-guided injection of medication in the intervertebral disc may reduce low back pain and postpone or avoid surgical intervertebral fusion. A retrospective study was performed in 8 non-operated surgical fusion candidates with painful monosegmental back disc after image-guided Discogel® injection at 3 months follow-up regarding the clinical outcome (clinical exam and questionnaires including VAS-, ODI- and SF-12 scores).

Results: Evaluation of SIJ MRI alone vs. both SIJ and spine MRI scored 11 vs. 15 of 32 patients with active SpA. These numbers were not statistically significant different and Cohen’s kappa demonstrated high agreement between both readers.
CBCT allows qualitative evaluation of ongoing fusion by gradual appearance of hazy densities (representing bone matrix calcification) around the cage, by disappearance of the radiolucent line between cage and vertebral endplates, and by increasing density of the bone graft filler over time. After Discogel® injection, the mean VAS-score improved from 5,8 to 3,4 (41%) and ODI-score improved from 38 to 25 (34%). Physical and mental component scores of the SF-12 questionnaire increased slightly.

Discussion and conclusions: Advanced imaging techniques play an important role in diagnosis, follow-up and image-guided intervention regarding spinal fusion. In this study, spine MRI in addition to SIJ MRI is not indicated for early diagnosis of active SpA. CBCT is a useful imaging technique to assess (ongoing) bony fusion following ACIF. Specific advantages inherent to CBCT are a high spatial resolution, a low radiation dose and few metal artefacts. Image-guided Discogel® injection improved patients’ pain and functional ability, thereby postponing fusion surgery.
Samenvatting

Inleiding: Medische beeldvorming wordt gebruikt voor de diagnose van ziektes, voor de opvolging van behandelingen of om medische interventies te begeleiden. Beenderige fusie tussen 2 wervels wordt bij volwassenen veroorzaakt door ziekte of door chirurgie. Het doel van de studie is om beeldvormingstechnieken te evalueren met betrekking tot intervertebrale fusie. Hiervoor werden er 3 klinische situaties gekozen waarbij medische beeldvorming werd onderzocht voor het vroeg diagnosticeren van een ziekte die leidt tot intervertebrale fusie, voor opvolging van een intervertebrale fusie operatie en bij een interventie om een fusie operatie uit te stellen.

Patiënten en methoden:

- Klinische situatie 1: Vroege diagnose van Bechterew (SpA) is zeer belangrijk voor het tijdig initiëren van een behandeling en MRI van het axiale skelet is hiervoor cruciaal. Is MRI van de sacroiliacale gewrichten (SIG) of van zowel de SIG en de wervelkolom nodig voor een vroege diagnose van SpA? 32 MRI onderzoeken werden geanalyseerd volgens de ASAS criteria door 2 onafhankelijke lezers. Cohen’s kappa en McNemar’s test werden uitgevoerd voor data analyse.

- Klinische situatie 2: Voor de opvolging van intervertebrale fusie operaties, zoals ACIF, wordt radiografie en CT gebruikt om te bepalen of er een succesvolle fusie of een pseudartrose aanwezig is. In een piloot studie werd cone-beam CT (CBCT) gebruikt voor een gedetailleerde beschrijving van de botvorming, 3 maanden na een ACIF operatie in 1 patiënt.

- Klinische situatie 3: Intradiscale injectie van medicatie, onder begeleiding van beeldvorming, helpt bij het verminderen van rugpijn en kan een chirurgische intervertebrale fusie uitstellen of vermijden. Een retrospectieve studie werd uitgevoerd met 8 kandidaten voor een fusie operatie met “painful monosegmental black disc”. De patiënten ondergingen een Discogel® injectie en hun klinisch resultaat werd onderzocht 3 maanden na de injectie (klinisch onderzoek en vragenlijsten waaronder VAS-, ODI- en SF-12-scores).

Resultaten: Evaluatie van MRI van de SIG vs. MRI van zowel SIG en wervelkolom toonde 11 vs. 15 van de 32 patiënten met actieve SpA. Dit verschil was statistisch niet significant en Cohen’s kappa gaf een hoge overeenkomst tussen beide lezers aan.

CBCT laat een kwalitatieve evaluatie toe van beenderige botfusie na een ACIF operatie door een geleidelijke verschijning van dense structuren (die bot matrix calcificatie voorstellen), door de verdwijning van de radiolucente lijn tussen de kooi en de wervels en door een toenemende densiteit van de botpasta.

Discogel® injectie verbeterde de gemiddelde VAS-score van 5,8 tot 3,4 (41%) en de ODI-score van 38 tot 25 (34%). De fysische en mentale component van de SF-12-score stegen geleidelijk.

Discussie en conclusie: Beeldvormingstechnieken spelen wat betreft wervelfusie een belangrijke rol in de diagnose, de opvolging en als begeleiding van interventies. Deze studie toonde aan dat MRI van de wervelkolom niet aanbevolen is voor de vroege diagnose van actieve SpA. CBCT is een bruikbare beeldvormingstechniek om de beenderige fusie te evalueren na ACIF operaties. Specifieke voordelen van CBCT zijn een hoge spatialie resolutie, een lage stralingsdosis en weinig metaalartefacten. Beeldvormings-begeleide injectie van Discogel® verbeterde de pijn en functionele activiteiten van de patiënten en stelde hierbij een intervertebrale fusie operatie uit.
1. Introduction

1.1 The spine: vertebrae and intervertebral discs

The major role of the spinal column is to provide support for the body. The spine consists of 33 individual vertebrae and is divided into 5 regions: 7 cervical vertebrae, followed by 12 thoracic vertebrae, 5 lumbar vertebrae, 5 sacral vertebrae and 4 vertebrae forming the coccyx. The upper 24 vertebrae are movable whereas the other ones are fused. The vertebral arch, which consists of 2 pedicles connecting 2 lamina to the vertebral body, is located posteriorly of the vertebral bodies and forms the spinal canal containing the spinal cord. The spinal cord gives rise to a total of 31 spinal nerve pairs. The spinal nerves exit the vertebrae under the vertebral pedicles through the intervertebral foramen and run through e.g. the legs in order to control sensation and movements. Each vertebra also contains 4 posteriorly located facet joints: one pair of facet joint connects to the vertebra above, whereas the other pair of facet joint connects to the vertebra below. Besides the 4 facet joints, 3 processes arise from each vertebrae: 1 spinous process and 2 transverse processes (figure 1A). The vertebrae are held together by strong fibrous bands, called ligaments (1).

The vertebral bodies are linked together by intervertebral discs (figure 1B). The main functions of the discs are to absorb shocks and to provide flexibility to the spine, allowing flexion, extension and rotation. The intervertebral disc is composed of a nucleus pulposus centrally and an annulus fibrosis peripherally (figure 1C). The nucleus pulposus consists of a gel-like substance containing proteoglycans, glycoproteins and collagen. The proteoglycans have the ability to attract and retain water and this enables the disc to absorb shocks during movements. The annulus fibrosus is a stiff structure consisting of collagen and elastin fibers organized in lamellae, structured concentrically surrounding the nucleus pulposus. The role of the annulus fibrosus is to provide support to the disc. Cartilaginous endplates of the vertebrae are located inferiorly and superiorly of the discs. A healthy adult disc contains some nerves which are mainly restricted to the outer one third of the annulus fibrosus. A few blood vessels are located in the annulus fibrosus part of the disc (2).

![Figure 1: Anatomy of the vertebral bodies and intervertebral discs](image)

A. Each vertebrae has 4 facet joints and 3 processes, located posteriorly of the vertebral body. B. Intervertebral discs are located between vertebral bodies. C. An intervertebral disc consists of an outer annulus fibrosus, composed of a stiff structure providing support, and an inner nucleus pulposus, consisting of a gel-like structure providing shock absorption. (Figure from Mayfield Clinic for Brain and Spine.)
Spinal fusion means the union of two or more vertebrae in order to form one solid piece of bone. The reason why vertebrae are joint together depends on the cause of fusion: through disease or through surgery. One disease which induces spinal fusion is inflammatory spondyloarthritis (SpA). In established stages of this disease, the spinal vertebrae gradually fuse, as a result of the inflammation characteristic of the disease. A second example of spinal fusion is fusion induced by a spinal fusion surgery. Spinal fusion surgeries involve techniques mimicking the normal healing process of broken bones aiming to joint two or more vertebrae together. These surgeries are most frequently performed in patients with degenerated intervertebral discs. Degeneration occurs as the disc ages: multiple changes happen and the disc can lose its height and can bulge. The main difference of these two examples of spinal fusion is that the vertebral fusion in patients with SpA is gained spontaneously due to the inflammatory feature of the disease, whereas an inflammation process is provoked by a surgery in order to form a bony fusion.

However, an intervertebral fusion surgery is a highly invasive procedure entailing several risks and possible complications. Therefore, recent research is based on discovering minimally invasive techniques to treat selected groups of patients with degenerated discs less invasively. An example of such a minimally invasive procedure is intradiscal Discogel® injection.

1.2 Axial spondyloarthritis

SpA comprises a group of inflammation diseases which share common characteristics: inflammation of the axial skeleton including the spine and sacroiliac joints (SIJ) (axial SpA) and/or peripheral joints (peripheral SpA) and the genetic association of the Human Leukocyte Antigen-B27 (HLA-B7) antigen (3). It is demonstrated that SpA has a genetic involvement, because the antigen HLA-B27 has a strong association with disease susceptibility. In the United Kingdom, 90 to 95% of patients with axial SpA are positive for HLA-B27. However, only 1 to 2% of HLA-B27 positive subjects develop the disease (4). Furthermore, the overall prevalence of SpA is estimated between 0,23% and 1,8% and men are 2 to 3 times more frequently affected than woman (5, 6).

The symptoms of axial SpA appear typically in the patient’s second to fourth decade of life (6). The most common clinical manifestation is inflammatory back pain. It is important to differentiate between inflammatory and non-inflammatory back pain in order to define the underlying cause. Inflammatory back pain is generally characterized by an insidious onset, stiffness of the back in the morning which improves with exercise and not by rest. In addition, inflammatory back pain is characterized by a significant pain relief in response to non-steroidal anti-inflammatory drugs (NSAIDs). Besides inflammatory back pain, buttock pain and gluteal pain, representing sacroiliac involvement, are also common symptoms of axial SpA. Furthermore, other clinical manifestations that are often associated with axial SpA are synovitis, enthesitis, dactylitis, uveitis and inflammatory bowel disease (3). SpA has a big impact on the quality of life and the patients often experience a reduced work ability (6).
The spectrum of axial SpA consists of non-radiographic SpA and Ankylosing Spondylitis (AS) (or Bechterew’s disease). Non-radiographic axial SpA is considered as the early stage of axial SpA and is characterized by acute inflammatory lesions to the SIJ and/or to the spine (3). The inflammation is the underlying cause of the inflammatory back pain. The inflammatory lesions are demonstrated as the presence of bone marrow edema (osteitis) in the peri-articular area of the SIJ or at subchondral areas of the vertebrae. Concerning these 2 areas, the peri-articular region of the SIJ is most frequently involved in axial SpA (7). AS on the other hand, is considered as the prototype of SpA and is the established stage of axial SpA. It is characterized by the presence of chronic structural changes to the SIJ and/or to the spine (3). Chronic inflammation of the SIJ or the spine leads to the development of erosions, sclerosis, joint space widening or narrowing, bony bridges in the SIJ or between the vertebral bodies (syndesmophytes), and finally spontaneous fusion (ankylosis) of the joint or vertebrae (figure 2). The onset of axial SpA is insidious, followed by a gradual progress to advanced stages of SpA. Moreover, the course of SpA is regarded as a fluctuating disease with variations in disease activity: episodes of flare, followed by more or less remission periods (6).

**Figure 2: T1- and T2-weighted sagittal MR image demonstrating an ankylosing spine and T1-weighted semicoronal MR image showing ankylosis of the sacroiliac joints (SIJ).** A: T1-weighted sagittal MR image of an ankylosing spine (white arrows) of a 60 year old man. B: T2-weighted sagittal MR image of an ankylosing spine (white arrows) of the same patient. C: T1-weighted semicoronal MR image of the SIJ demonstrating ankylosis (white arrows) and massive fat infiltration in both SIJ. (Figure C from Ostergaard M. et al.; Magnetic resonance imaging in spondyloarthritis-how to quantify findings and measure response)

### 1.3 Spinal disc disorders

Spinal disc disorders are common causes of chronic neck and low back pain (LBP). Most disc disorders are located in the cervical or lumbar part of the spine (2). Depending on the level the disc disorder is located, patients experience neck pain (when the disc disorder occurs in the cervical spine) or LBP (when the disc disorder is located in the lumbar spine). Nowadays, neck pain has an overall prevalence of 27% (8). C6-C7 is most commonly involved (60%), followed by C5-C6 (25%) (9). Patients with neck pain often experience pain radiation into their shoulders or arms. LBP is also a common health problem with an estimated prevalence of 18% (10). LBP can cause radiculopathy as
well. The most prevalent type of LBP is discogenic LBP, accounting for 39% of the cases (11). Besides the health problem neck pain and LBP cause, they also entail large socio-economic problems, leading to both direct costs and indirect costs, such as a reduced productivity at work. The pain extremely affects the life quality of the patients, thereby causing many patients to quit working.

Degenerative disc changes are the most common spinal disc disorder. Degeneration of intervertebral discs is a result of the natural aging process. With increasing age and degeneration, the morphology of the disc becomes more and more disorganized and proteoglycans become degraded. This degradation is responsible for the consequent reduction in osmotic pressure and loss of hydration in the nucleus pulposus. Subsequently, the disc loses its height which can lead to disc bulging (2). In addition, an increased vascular and neural ingrowth is demonstrated in degenerate discs and this is found to be associated with chronic neck or back pain (12).

Disc degeneration often leads to the onset of other structural changes, such as osteophyte formation, spondylolisthesis and herniated discs (figure 3). The formation of osteophytes or bone spurs can arise from vertebral endplates, vertebral facet joints or uncovertebral joints. Osteophytes can induce spinal canal narrowing (stenosis) with subsequent impingement on the spinal nerve or spinal nerve roots, which is a common cause of radiculopathy (13-16). Disc degeneration may also be associated with spinal instability, such as spondylolisthesis (17). Furthermore, a herniated disc occurs when a weak area or a tear in the annulus fibrosus allows the gel-like material within the nucleus to leak into or through the outer layers of the annulus fibrosus. A disc protrusion is the condition when the outer layers of the annulus fibrosus are still intact and none of the nucleus pulposus content is escaped beyond the outer layers of the annulus fibrosus. The condition in which a tear in the annulus fibrosus induces chronic back pain is also called painful monosegmental black disc (PMBD). Advanced stages of disc protrusions, when the nucleus pulposus material escaped beyond the outer layers of the annulus fibrosus, are disc herniations. A disc herniation can result in impingement on spinal nerve roots. Some studies hypothesized that molecules in the outer region of the annulus fibrosus are responsible for the pain because they are able to sensitize the nerve roots (2, 17). Other studies, however, hypothesized that the intervertebral discs of patients with chronic LBP have nociceptive nerve endings extending into the inner third of the annulus fibrosus and even in the nucleus pulposus, whereas only the outer third of the annulus fibrosus is innervated in healthy discs. Therefore, these studies assumed that the ingrowth of nerve endings and blood vessels contributes to the pathogenesis of discogenic pain (12, 18).
Figure 3: Spinal disc disorders presented on the lumbar spine. Degenerative disc changes occur when discs age. Degeneration of discs can lead to disc bulging, herniated discs, thinning of the discs, it can induce the formation of osteophytes (bone spurs) and can induce spondylolisthesis (black arrow). (Figures adapted from www.spineuniverse.com)

1.3.1 Intervertebral fusion surgery as a treatment option

The majority of patients with discogenic pain can be cured with non-surgical treatments including physical therapy and medications such as NSAIDs. When these conventional therapies fail, a spinal fusion surgery is often considered in order to relief the pressure on spinal nerves and subsequent reduction of discogenic pain. A spinal fusion is performed in order to join two or more vertebrae together using bone graft filler and surgical materials. Anterior cervical interbody fusion (ACIF) is a frequently performed spinal fusion surgery. During an ACIF procedure, the damaged disc is completely removed (discectomy) and the empty space is replaced with autograft, allograft or a cage with an artificial substitute in order to maintain the disc height. Most surgeons in this hospital (Ziekenhuis Oost-Limburg, Genk, Belgium) prefer using a cage (interbody implant) filled with an artificial substitute. In order to provide more stability, the vertebrae can subsequently be fixated with an anterior plate and screws. The function of the cage and the artificial substitute is to maintain disc height and to stimulate bone healing aiming to create an intervertebral fusion between the two adjacent vertebrae and to form one solid piece of bone. A successful fusion is expected to lead to a good clinical result. A successful fusion requires a continuous trabecular bone bridge between the vertebrae of the operated level(s) and the inability of these vertebrae to move. This is accomplished on average after 3 to 6 months (19). Histologically, the process of osseointegration exists of 3 stages: the inflammation stage (week 1 to 3), followed by the repair stage (week 4 to 5) and the remodeling stage (after week 5). The early inflammation stage is initiated after bleeding injury to the endplates during surgery, followed by the release of inflammatory factors and the formation of a cartilage scaffold. The repair stage is characterized by differentiation of mesenchymal cells into chondroblasts and osteoblasts which produce immature bone by deposition of calcium phosphate. This process is called calcification or mineralization. During the remodeling phase, which can last several years, osteoblasts continue to deposit osteoid, resulting in the formation of new compact bone (20).
There are 4 main types of cages which are frequently used in this hospital: cages provided by Zimmer, Cormed, Pioneer and DePuy Synthes. The surgical devices can be constructed of different materials (table 1). Zimmer cages are constructed of trabecular metal (tantalum), which are radiopaque, porous implants and have bone-like physical and mechanical properties enabling bone infiltration. Cormed cages, on the other hand, are made of polyether ether ketone (PEEK) with a titanium coating (Titanium Sputtered Coating (TSC)). The titanium coating enhanced the implants biocompatibility and stimulates the bone-implant integration. Because the cage is not radiopaque, it contains two radiopaque tantalum markers which are indispensable during the surgery procedure for correct placement of the cage. The traditional cages of Pioneer are composed of PEEK, whereas the new type of Pioneer cages are composed of nanocrystalline hydroxyapatite. This material would be superior to PEEK cages as they provide an equivalent composition and structure to the mineral component of bone, an increased osteoblast attachment and increased radiopacity. A titanium anterior plate and titanium screws are used for extra stabilization. Cages of Synthes are constructed of PEEK with tantalum markers and titanium plating and screws. The surface of the PEEK implant contains teeth-like protrusions providing initial stability. The main characteristic of the Synthes cages is that the cage and the fixation (screws) fit completely within the disc space.

Table 1: Materials and image of the main types of cervical interbody cages used in Ziekenhuis Oost-Limburg for anterior cervical interbody fusion surgeries.

<table>
<thead>
<tr>
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<th>Zimmer TM cage</th>
<th>Cormed TSC cage</th>
<th>Pioneer NanOss cage</th>
<th>DePuy Synthes Zero-P cage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Material</td>
<td>Trabecular metal (tantalum)</td>
<td>PEEK + titanium coating</td>
<td>Nanocrystalline hydroxyapatite</td>
<td>PEEK</td>
</tr>
</tbody>
</table>

An ACIF surgery entails several risks and complications. In addition, fusion surgeries immobilize a part of the spine resulting in a higher stress and strain on the adjacent intervertebral joints. An increased rate of disc degeneration at the adjacent levels is seen (21).
1.3.2 Minimally invasive intradiscal Discogel® injection as a treatment option for young active patients

Intervertebral fusion surgeries can also be performed in the lumbar spine (including anterior lumbar interbody fusion (ALIF), posterior lumbar interbody fusion (PLIF), transforaminal lumbar interbody fusion (TLIF) and extreme lateral interbody fusion (XLIF)). However, due to the risks and complications these surgeries entail, recent research is based on the development of minimally invasive techniques in order to relieve discogenic pain and to prevent a surgery. Minimally invasive therapies have the advantage of having low costs, short hospital stay and it can be repeated several times in the same patient. Especially in young, active patients with PMBD, minimally invasive treatments are recommended in order to prevent a surgery.

Percutaneous intradiscal injection of Discogel® is considered a minimally invasive treatment aiming to reduce the discogenic pain. Discogel® is a CE labeled product. The active component of Discogel® is ethyl alcohol and the exact working mechanism of Discogel® is not completely understood (22). Prior to performing the injection, discography allows to correlate the discogenic pain with a particular disc level. The key characteristic of discography is based on the induction of concordant pain as a reaction to disc stimulation. This procedure consists of fluoroscopy-guided insertion of a needle into the disc center and the subsequent injection of a contrast solution. The injection increases the intradiscal pressure. If the patient experience concordant pain, which means similar pain, it can be confirmed that that particular disc level is the source of the pain. Discogel® also consists of a contrast substance, tungsten, which enables visualization of the annulus tear on a Computed Tomography (CT) discography of the patient (supplemental information S1 1) (23).

1.4 Medical imaging of the spine

Medical imaging plays an important role in diagnosing diseases, in the follow-up of treatments and to guide interventions regarding spinal fusion. Plain films are the first-line imaging technique to detect spinal changes. Besides plain films, CT and Magnetic Resonance Imaging (MRI) are also frequently used in visualization of the spine and spinal changes.

1.4.1 Plain films and CT

The advantages of plain films, including low cost, reproducibility, low radiation dose and possibility of standing flexion and extension images, are characteristics which made plain films a widely used imaging modality to visualize spinal changes. They can be performed in different planes: anteroposterior, lateral and flexion and extension views.

In the past, radiological diagnosis of axial SpA was performed based on plain films. Besides the radiologic evidence of sacroiliitis, the diagnosis of axial SpA was also based on clinical features and laboratory findings (HLA-B27 and C-Reactive Protein (CRP)-value). In order to detect SpA radiographically, the modified New-York Classification Criteria, established in 1984, were the most widely used criteria on plain films (supplemental information S1 2) (24). With regard to visualization of structural changes to the spine, erosions of the vertebrae are demonstrated on radiographs by
Active sacroiliitis is characterized by acute inflammatory lesions which can be visualized on MRI examinations. Radiographic sacroiliitis, with syndesmophytes in advanced stages, is characterized by chronic structural lesions which are visible on plain films or CT-scans. However, it is known that definite radiographic sacroiliitis (structural changes) is not present in the early stages of axial SpA and therefore, diagnosis can be delayed up to 5-10 years after the onset of symptoms (25). In this way, only patients with AS will be diagnosed and patients with non-radiographic SpA will be overlooked. Therefore, plain films cannot exclude the possibility of SpA. The diagnostic delay and low sensitivity of plain films has been the rationale in developing new criteria for the diagnosis of axial SpA.

Another purpose for which plain films are used is the evaluation of the osseointegration following spinal fusion surgeries. The radiographic outcome is important in order to determine whether the procedure was successful or not. Plain films are the first-line imaging technique for this purpose. Radiologists can use the Food and Drug Administration (FDA) criteria in order to define a successful fusion or arthrodesis: evidence of trabecular bone bridging between the involved vertebrae, an angular motion of less than 5° and a translational motion of less than 3 mm on flexion/extension plain films (26). The angular and translational motion define the mobility of the vertebrae. A limitation of using plain films as an assessment of osseointegration and bony fusion is the superposition of structures. This can impede the evaluation of bony fusion in the disc space around the cage and makes it impossible to visualize the bone graft filler in radiopaque cages.

CT is another imaging technique frequently used for the post-operative evaluation of spinal fusion surgeries due to the enhanced visualization of bone tissue and its 3-dimensional reconstructed images. Correct position and integrity of the anterior plate and screws is often evaluated on CT-scans. CT imaging is reported to have a higher accuracy and provides a more detailed picture of the spine in comparison to plain films (27). A limitation of CT-scanning is that the presence of metallic screws and plates can cause artefacts on the images. Good positioning of the patient i.e. the cage in the middle of the CT bore and as much as possible parallel with the middle of the X-ray beam, attempts to diminish the metal artefacts. However, metal artefacts interfere with the image quality of CT-scans and can impede reliable evaluation (27).

### 1.4.2 MRI to diagnose axial spondyloarthritis and painful monosegmental black disc

![Diagram showing imaging techniques to diagnose axial SpA in the different stages of the disease.](image)

**Figure 4: Imaging techniques to diagnose axial SpA in the different stages of the disease.** Active sacroiliitis is characterized by acute inflammatory lesions which can be visualized on MRI examinations. Radiographic sacroiliitis, with syndesmophytes in advanced stages, is characterized by chronic structural lesions which are visible on plain films or CT-scans.
During the last years, MRI has proven to be more sensitive than plain films in evaluating the SIJ and spine as it enables early diagnosis of axial SpA by visualization of early, acute, inflammatory changes as well as chronic structural lesions of SpA (figure 4) (28). In addition, early diagnosis is important because treatment is more effective if it is used in early stages of the disease (29). Therefore, the introduction of MRI as an imaging technique to detect active axial SpA has been an advancement with regard to early diagnosis of SpA.

In 2009, the Assessment of SpondyloArthritis international Society (ASAS) had developed new classification criteria for axial SpA in order to classify or diagnose SpA, for patients with (AS) and without radiographic sacroiliitis (figure 5) (30). The most important development compared to previous classification criteria is the implementation of MRI positivity of sacroiliitis as a criterion, resulting in a sensitivity of 82.9% and a specificity of 84.4%. The ASAS classification criteria are established to be applied for patients suffering 3 or more months from back pain with an age of onset before 45 years and they have 2 arms: an imaging arm and a clinical arm. The imaging arm requires the presence of sacroiliitis demonstrated by radiographs or MRI and at least one typical clinical feature of SpA. The clinical arm on the other hand requires the presence of HLA-B27 and at least 2 typical clinical features of SpA. Typical clinical features of SpA include inflammatory back pain, arthritis, enthesitis, uveitis, dactylitis, psoriasis, Crohn’s disease or ulcerative colitis, good response to NSAIDs, family history of SpA, HLA-B27 positivity, elevated CRP. A patient is diagnosed as positive for axial SpA if the patient meets one of the two arms of the ASAS criteria (5, 31).

### ASAS CLASSIFICATION CRITERIA FOR AXIAL SPONDYLOARTHRITIS (SpA) (2009)

MRI: sensitivity 82.9%; specificity 84.4%

For patients suffering ≥ 3 months from back pain with age of onset < 45 years

**Imaging arm**

- Sacroiliitis on imaging
  - acute inflammation on MRI highly suggestive for sacroiliitis associated with SpA, or
  - definite radiographic sacroiliitis according to the Modified New York criteria

**Clinical arm**

- HLA-B27 positivity
  - familial history of SpA

<table>
<thead>
<tr>
<th>SpA features</th>
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<th>SpA features</th>
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<tr>
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<td>- HLA-B27 positivity</td>
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<td>- psoriasis</td>
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<td>- Crohn’s/collitis</td>
<td>- good initial response on NSAIDs</td>
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<tr>
<td>uveitis</td>
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**Figure 5: Diagnosis of axial spondyloarthritis (SpA) according to the Assessment of SpondyloArthritis international Society (ASAS) classification criteria (2009) by the imaging arm or clinical arm.** The imaging arm requires evidence of sacroiliitis on MRI or plain films in combination with minimal 1 SpA feature, whereas the clinical arm requires HLA-B27 positivity and minimal 2 SpA features for the diagnosis of axial SpA. HLA = Human Leukocyte Antigen, NSAIDs = Non-Steroidal Anti-Inflammatory Drugs, CRP = C-reactive protein
MRI is also used for the diagnosis of patients with discogenic LBP, together with discography. Discs containing tears in the annulus fibrosus have a dehydrated nucleus pulposus, thereby causing the discs to appear dark and black on MR images (supplemental information SI 1) (23).

1.4.3 Cone-beam CT to assess osseointegration following cervical interbody fusion surgeries

A novel potential imaging method to determine osseointegration following ACIF surgeries is a different type of CT, namely cone-beam CT (CBCT). The first commercial CBCT-scanner, being introduced in 1998, was used for dental imaging (32, 33). However, due to the development of larger bore CBCT devices, CBCT can be applied to other areas of the human body such as the head- and neck region. CBCT-scanning has several advantages in comparison with the classical CT. A first advantage of CBCT over conventional CT, is that in general, a higher resolution is provided, namely 150 μm (34). The second advantage is the use of a cone shaped X-ray beam resulting in a lower radiation exposure compared to the classical CT, with effective dose values ranging from 13 to 82 μSv for CBCT devices and from 474 to 1160 μSv for Multi-Slice CT (MSCT) devices (35). The conventional CT in contrast, uses a fan X-ray beam which rotates around the patient resulting in axial slices. By performing many rotations around the patient, a complete image is formed, with gaps of information between the rotations. Software programs stitch the images together to form a complete image of the body. The repeated rotations results in a relative high radiation dose (36). In addition, metal artefacts are less abundant on CBCT-scans compared to CT-scans (37). Metal artefacts are in particular caused by surgical hardware including cages, metal anterior plating and screws.

1.5 Study aims

The hypothesis of this research is that advanced radiological techniques may lead to precise assessment of the spinal fusion process or to postpone surgical spinal fusion. Three clinical situations will be investigated in order to support this hypothesis (figure 6).

The first study is a retrospective study concerning early diagnosis of active axial SpA. The research question of this study is whether MRI of the SIJ alone or MRI of both the SIJ and the spine is necessary to diagnose patients with active axial SpA. In order to answer this research question, MRI examinations of 32 patients will be investigated for active inflammatory axial SpA based on SIJ MRI examination alone vs. both SIJ and spine MRI examination according to the ASAS criteria. The study aim is to investigate whether MRI of the SIJ needs to be extended in all patients with an additional MRI of the spine for a reliable diagnosis of active axial SpA.

Secondly, the attention will be focused on the assessment of the bone fusion process after ACIF surgeries using CBCT. A pilot/feasibility study will be performed in order to answer the question whether CBCT is a useful imaging technique for the radiological follow-up of ACIF surgeries. Until now, plain films and CT images are used for the assessment of osseointegration after ACIF procedures, the latter one causing a relative high radiation dose. This part of the study aims to
reduce the patients’ radiation dose during the follow-up by using CBCT imaging. Three objectives will be considered in order to answer this second research question. The first objective is to attempt to describe the ongoing bone fusion process based on plain films and CBCT images of a patient who underwent an ACIF procedure using a Cormed TSC implant, with a follow-up of 3 months. Afterwards the radiation dose of the CBCT-scanner will be compared to the radiation dose of the CT-scanners in this hospital. Lastly, the presence of metal artefacts caused by different types of cages on CBCT will be investigated in order to find the best cage material which does not interfere with the image quality.

The third study concentrates on the clinical effect of image-guided intradiscal injection of Discogel®. The research question is whether intradiscal Discogel® injection is an effective minimally invasive treatment for young, active adults with lumbar PMBD in order to postpone a spinal fusion surgery, regarding the clinical outcome and economic effect. The first research objective is to investigate the clinical outcome in 8 patients, 3 months after intradiscal Discogel® injection. The second objective is to estimate the economic effect compared to a lumbar interbody fusion surgery.

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**Figure 6: Overview of the research questions of the 3 studies described in this report.** This report focusses on spinal fusion, acquired through disease (SpA) or surgery (ACIF) and a minimally invasive technique to postpone surgery (Discogel® injection). It comprises a comparative study aiming to define whether MRI of the SIJ alone or MRI of both SIJ and spine is necessary for a reliable early diagnosis. The second study aims to describe CBCT as a novel imaging technique to evaluate the ongoing bony fusion process following ACIF surgeries. The third study aim is to evaluate the clinical outcome of 8 patients at 3 months after intradiscal Discogel® injection. SpA = SpondyloArthritis, MRI = Magnetic Resonance Imaging, SIJ = Sacroiliac Joint, ACIF = Anterior Cervical Interbody Fusion, CBCT = Cone-beam CT.
2. Subjects and methods

2.1 Early diagnosis of axial spondyloarthritis using MRI

2.1.1 Subjects

This retrospective study was conducted with MRI examinations of 32 patients (mean age 43 year, 8 male and 24 female) suspected to have axial SpA based on clinical symptoms and who got 2 MRI-scans: one of the SIJ and one of the spine. A large part of the subjects got multiple MR images at different time points, resulting in a total of 86 MR examinations of the SIJ and the spine. All MR images were performed between November 2009 and April 2014 in the hospital Ziekenhuis Oost-Limburg at the department of radiology.

2.1.2 MRI

Each patient was subjected to an MRI of the SIJ and one of the spine. The MRI of the SIJ included paracoronal T1-weighted, paracornonal and para-axial T2-weighted with fat saturation. The MRI protocol of the spine included the following sequences, sagittal T1-weighted sequence without contrast enhancement and sagittal T2-weighted short tau inversion-recovery (STIR) sequence.

2.1.3 Assessment of axial spondyloarthritis according to the ASAS criteria

The MR examinations of the SIJ and the spine were analyzed by 2 independent readers according to the ASAS criteria for axial SpA in order to assess the number of subjects who had an acute inflammation phase of axial SpA. Areas of subchondral inflammation were analyzed on T2-weighted STIR images as hyperintense areas and as hypointense areas on T1-weighted images. An ASAS positive MRI of the SIJ was defined as the presence of peri-articular bone marrow edema highly suggestive of sacroiliitis on 1 place on minimal 2 consecutive slices or on 2 or more places which are present on 1 slice (figure 7A and B). A positive MRI of the spine was defined as minimal 3 places of bone marrow edema, each on minimal 2 consecutive slices (figure 7C). Spinal lesions include corner inflammatory lesions and bone marrow edema in the facet joints. Structural lesions including fat infiltration, erosions, sclerosis or ankylosis, which are best visualized on T1-weighted images, were not sufficient to indicate the MRI as an ASAS positive image (38). Firstly, the readers evaluated the SIJ MRI and then the spine MRI. In this way, the outcome for the MRI examination of the SIJ alone was not affected by the MRI examination of the spine. The combined SIJ MRI and spine MRI evaluations were considered ASAS positive if the SIJ MRI and/or the spine MRI was ASAS positive.
Figure 7: T1- and T2-weighted short tau inversion recovery (STIR) paracoronal MR images of the sacroiliac joints (SIJ) of a 47 year old man and T2-weighted STIR sagittal MR image of the spine of a 56 year old man. A: T1-weighted MRI of the SIJ demonstrating inflammatory lesions (bone marrow oedema, osteitis) (arrows) as hypointense areas. B: T2-weighted STIR MRI of the SIJ showing hyperintense inflammatory lesions in the peri-articular area (arrows). This image is positive for axial SpA according to the ASAS criteria. C: T2-weighted STIR MRI of the spine demonstrating 2 hyperintense corner inflammatory lesions (arrows).

2.1.4 Data analysis

Cohen’s kappa coefficient was calculated in order to evaluate the concordance or inter-rater variability between the two readers analyzing SIJ and spine MR images according to the ASAS criteria. Cohen’s kappa was interpreted according to the Landis and Koch scale: a score between 0 and 0,20 was indicated as very low concordance; between 0,21 and 0,40 as low concordance; between 0,41 and 0,60 as moderate concordance; between 0,61 and 0,80 as satisfactory concordance; and between 0,81 and 1 as excellent concordance.

Because the data of all images cannot be considered independent because multiple MR images were derived from the same patient, each patient was allocated a ‘positive’ or ‘negative’ in order to collect 2 ultimate results for each subject: one for the SIJ and one for the spine. The ultimate result was ‘positive’ when one image of a patient was positive according to the ASAS criteria. Only when all
images of the same subject were reviewed negative, then the ultimate result was ‘negative’.

Statistical analysis was performed using SPSS Statistics 22 Software (IBM). In order to examine whether there was a difference between the number of ASAS positive subjects regarding evaluation of the SIJ MRIs and SIJ and spine MRIs, crosstabs were constructed. Furthermore, a McNemar’s test was performed in order to investigate whether the difference between both groups was significant ($\alpha < 0.05$).

2.2 Cone-beam CT for the radiological follow-up of cervical fusion surgeries

2.2.1 Subject

A 43 year old female patient presented at our hospital with neck pain and radiculopathy. Clinical evaluation and MRI was performed in order to diagnose the patient with disc herniation at the level of C5-C6. Initial treatment consisted of 3 cervical epidural infiltrations at the involved disc level. However, insufficient response was observed. After obtaining an informed consent, the patient was included in this study and the ACIF procedure was performed using an Orthobion’s TSC cage following the instructions of the manufacturer. The involved vertebrae were subsequently fixated with titanium anterior plating and screws. No complications were reported during the surgery and the patient was discharged the day after the procedure.

2.2.2 Cone-beam CT

The CBCT in our hospital, NewTom 5G CBCT (QR Srl, Verona, Italy), was used for this research. By adjusting the height of the table, the patient was positioned with the cage in the middle of the CBCT bore and as parallel as possible with the middle of the conic X-ray beam in order to take a CBCT-scan of the cervical spine. Therefore, a field of view of 12x8, a spatial resolution of 150 µm and reconstructed axial images with an isotropic resolution of 0.5 mm was used. Images were reformatted in coronal and sagittal planes with a width of 1 mm and intervals at 1 mm.

2.2.3 Radiological follow-up

Assessment of bony fusion following the ACIF surgery was performed based on evaluation of plain films and CBCT-scans. Different imaging planes were used for the plain films of the cervical spine: anteroposterior view, lateral view and dynamic flexion and extension views. The anteroposterior images and lateral images were performed at 1 day, 6 weeks and 3 months after the surgery; the flexion and extension images were only performed 3 months post-surgery. CBCT-scans were performed at 1 day, 6 weeks and 3 months after the surgery. The evaluation of the integrity of the instrumentation, trabecular bone formation, radiolucent line and subsidence were performed based on the plain films and the CBCT-scans. The density of the bone graft filler was evaluated on the CBCT images and angular and translational motion was assessed on flexion and extension plain films at 3 months follow-up.
Evaluation of trabecular bone formation, the radiolucent line and the density of the bone graft filler was described qualitatively. Subsidence was measured as the difference between the heights of the upper endplate of the superior vertebral body to the lower endplate of the inferior vertebral body of the operated level(s) at 1 day post-operatively and 3 months after the procedure (figure 8A). This distance was measured anteriorly and posteriorly. Subsidence was noted when the height was reduced more than 2 mm at follow-up. However, the magnification has to be taken in consideration when measurements are compared on plain films. In order to calculate the magnification factor, the length of the anterior plate was measured on the plain films. The angular motion of the vertebral bodies adjacent to the operated disc was calculated by measuring the Cobb angle on flexion and extension plain films. The Cobb angle is the angle between the line parallel to the upper endplate of the superior vertebral body and line parallel to the lower endplate of the inferior vertebral body of the operated level(s) (figure 8B). Angular motion was regarded as the difference between the measured Cobb angle in flexion and extension views. No mobility was assumed when the angular motion was less than 3°. In order to measure the translational distance, the following steps were followed. Firstly, a line tangent to the upper endplate of the inferior body was drawn. Then a perpendicular second line was drawn through the upper posterior corner of the inferior vertebral body. Next, the distance between the lower posterior corner of the superior vertebral body and the second line was measured, parallel to the first line (figure 8C). The translational motion was regarded as the difference between this distance on flexion and extension plain films. Mobility was assumed when this distance was more than 5 mm.

**Figure 8: Measurements of subsidence, angular motion and translational motion.** A: In order to assess subsidence, the anterior and posterior distance between the upper endplate of the superior vertebral body and the lower endplate of the inferior vertebral body of the operated level(s) was measured. Subsidence was noticed as the difference of these heights at 1 day and 3 months post-surgery was more than 2 mm. B: Angular motion was regarded as the difference of the Cobb angle of the operated level on flexion and extension images. The Cobb angle was measured as the angle between the line tangent to the upper endplate of the superior vertebral body and the lower endplate of the inferior vertebral body of the operated level(s). C: Translational motion was measured as the distance between the lower posterior corner of the superior vertebral body and the upper posterior corner of the inferior vertebral body parallel to the line tangent to the upper endplate of the inferior vertebral body. Translational motion was assessed based on the change of this distance on flexion and extension images (black arrow).
2.2.4 Clinical follow-up

The clinical outcome of the patient was assessed using questionnaires concerning pain intensity and functional disability (disability to perform daily activities). Pain intensity for neck pain, right arm pain and left arm pain was assessed using the Visual-Analogue-Scale (VAS)-score. Therefore, the patient was asked to mark the intensity of her pain on a 10 cm line, providing a range of scores between 0 and 10 (supplemental information S2 1). Functional disability was evaluated by the Neck-Disability-Index (NDI)-score. The NDI-score measures neck-specific disability and it was calculated using a 10-item questionnaire (supplemental information S2 2). The questionnaires were filled out at the different time points: pre-operatively, 6 weeks post-surgery and 3 months post-surgery.

2.2.5 Comparison of radiation doses of CT and cone-beam CT

Computed Tomography Dose Index (CTDI)-values of all patients who received a CT- or CBCT-scan of the cervical spine at our hospital between the period of June 2014 and September 2014 were collected. The CTDI-values of the CBCT device was compared to 4 CT devices (Definition, Siemens; Somatom Definition AS64 fast care, Siemens; and 2 devices of Somatom Emotion 6, Siemens). The median value of the CTDI-value of every device was calculated. The difference in size of field of view was taken into account by dividing the CTDI-values of the CBCT by 2.

2.2.6 Comparison of metal artefacts caused by different types of cervical interbody cages

In order to compare the metal artefacts on CBCT-scans caused by the 4 different types of cervical interbody devices which were used in this hospital, minimal 2 CBCT-scans for each cage were collected. The radiodense or radiolucent artefacts were described qualitatively for each cervical cage.

2.3 Clinical outcome of minimally invasive Discogel® injection

2.3.1 Subjects

A total of 8 patients (mean age 38 year, 6 male and 2 female) with PMBD, which were unresponsive to conservative therapy, were included for this study within 11 months. Conservative treatment consisted of medications, epidural infiltrations or kinesitherapy. At baseline, all patients underwent physical examination by a neurosurgeon and a radiological evaluation based on lumbar MRI examination. All patients demonstrated a black disc on the images of the lumbar spine and were diagnosed with PMBD. The lumbar level was L3-L4 in 2 cases, L4-L5 in 3 cases, L5-S1 in 2 cases and L4-L5 and L5-S1 in 1 case.

2.3.2 Discogel® administration procedure and discography

The patients were positioned prone and the Discogel® injection was performed percutaneously under fluoroscopic guidance. Discography ensured that the expected disc level indeed induced the pain. A concordant pain response was achieved in 1 level in 7 patients and in 2 levels in 1 patient as a result of the discography (the same levels as diagnosed with MRI). Discogel® injection consisted of
fluoroscopy-guided injection of 0,4-0,8 ml Discogel® for each injected level. No adverse events were reported during and after the Discogel® injection procedure.

2.3.3 Clinical follow-up

All 8 patients returned for follow-up visits at 3 weeks, 6 weeks and 3 months after the injection. During these follow-up meetings and at 1 day post-injection, the patients were asked to fill out questionnaires in order to calculate pain intensity, limitation to daily activities and the mental and physical health from the patients’ point of view. Pain intensity was determined using the VAS-score by which the patients had to note the mean intensity of the pain on a 10 cm line in which 0 cm means no pain and 10 cm means the worst imaginable pain (supplemental information S2 3). Oswestry-Disability-Index (ODI)-score was used to determine the limitation to daily activities based on 10 questions (supplemental information S2 4). The mental and physical health scores were calculated using Short Form-12 (SF-12) questionnaires (supplemental information S2 5). The questionnaires were analyzed by a person who was unaware of the clinical condition of the patients.

2.3.4 Estimation of the economic effect

Besides filling out the questionnaires during the follow-up meetings, the clinical condition was discussed and change in work status and/or sport-activities was noted. Furthermore, a patient invoice of a general single-level lumbar interbody fusion surgery was compared with invoices of Discogel® injection in order to estimate the economic effect between a Discogel® injection and a lumbar interbody fusion surgery.
3. Results

3.1 Early diagnosis of axial spondyloarthritis using MRI

Firstly, the agreement between the two readers was examined regarding the application of the ASAS criteria for MRI evaluation. An excellent agreement between the two readers was found. Cohen’s kappa demonstrated a value of 0,873, indicating an excellent concordance between the two readers according to the Landis and Koch scale. There was a disagreement in 5,2% of total number of images.

Secondly, the number of patients with active SpA was calculated based on MR examination of the SIJ alone vs. MR examination of both SIJ and spine. Crosstabs of both readers comparing the ASAS outcome of the SIJ MR examinations and the ASAS outcome of both SIJ and spine MR examinations revealed that reader 1 indicated 11 patients as ASAS positive investigating the SIJ MRIs, whereas 15 patients were ASAS positive when the SIJ and spine MRIs were evaluated (table 2). Reader 2 evaluated 14 and 18 ASAS positive patients, respectively investigating the SIJ MRIs and the SIJ and spine MRIs. These results show that both readers found 4 more patients (12,5%) with active SpA when they evaluated the MRI of the spine in addition to the MRI of the SIJ, which means that the MRIs of these patients were ASAS negative for SIJ and ASAS positive for the spine. The 4 patients of reader 1 were the same as those of reader 2. These patients (12,5%) will be overlooked when the patients were subjected to MRI of the SIJ alone (figure 9).

Table 2: Crosstabs demonstrating the outcomes of reader 1 and reader 2 regarding the evaluations of the MR images of the sacroiliac joints (SIJ) and the MR images of both the SIJ and the spine according to the ASAS criteria.

<table>
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Figure 9: Pie chart illustrating the outcome of MRI evaluation of the sacroiliac joints (SIJ) and MRI evaluation of the spine of reader 1 according to the ASAS criteria for axial spondyloarthritis (SpA). The blue part (12,5%) represents the patients whose MRIs of the SIJ were negative, whereas the spine MRIs were positive according to the ASAS criteria. These patients would be missed if only the SIJ was investigated.

Next, it was investigated whether the difference between the number of ASAS positive subjects, based on MR examination of the SIJ alone and MR examination of both SIJ and spine, was significantly different using a McNemar’s test. The test revealed no statistically significant difference between the number of ASAS positive subjects of both groups (P-value = 0.125 for both readers).

3.2 Cone-beam CT for the radiological follow-up of cervical fusion surgeries

3.2.1 Integrity of instrumentation

The plain films and CBCT-scan of 1 day after the procedure showed a good placement of the cage, anterior plate and screws (figure 10 and 11). The plain films and CBCT-scans at 6 weeks and 3 months follow-up demonstrated still a good cage position and no screw or anterior plate fractures.

3.2.2 Trabecular bone bridge formation

Qualitative analysis of the plain films and CBCT images of 1 day post-surgery demonstrated the presence of bone spurs posteriorly at the superior and inferior endplates of the involved disc level (figure 10B and 11A and B). No trabecular bone bridge was observed at the lateral plain films and CBCT-scans at 6 weeks and 3 months post-operative follow-up. Regarding bone formation assessment within the disc space around the cage, the lateral plain film and sagittal CBCT image of 6 weeks follow-up showed bone apposition posteriorly at the upper endplate, as represented by radiodense thickening of the endplate.
Figure 10: Plain films demonstrated the ongoing bone fusion process after anterior cervical interbody fusion surgery over time. Plain films in anteroposterior (A) and lateral (B) views of 1 day, 6 weeks and 3 months post-operatively showed good position and integrity of the cage, anterior plate and screws and provided qualitative analysis of the bony changes by bone apposition posteriorly of the vertebral endplates of the operated level (white arrows) and the gradual disappearance of a radiolucent line superior to the cage over time (white circle).

In addition, the sagittal and coronal CBCT images of 6 weeks post-surgery showed the appearance of hazy densities posterior and lateral of the cage, which could represent matrix calcification. The hazy densities were still present at 3 months of follow-up, as shown on sagittal and coronal images. Axial images also showed the occurrence of hazy densities in the disc space around the cage, in particular on the left side, which became more radiodense at 3 months post-surgery.
Figure 11: Cone-beam CT (CBCT) images enabled qualitative analysis of the bone fusion process after anterior cervical interbody fusion surgery over time. CBCT images in coronal (at the height of the left (A) and right (B) screw), sagittal (C) and axial (D) views at 1 day, 6 weeks and 3 months post-operatively provided assessment of the integrity of the cage, plate and screws and qualitative assessment of the bony changes by bone apposition posterior of the vertebral endplates of the operated level (white arrows) and the appearance of hazy densities in the disc space around the cage (black thin arrows), the disappearance of a radiolucent line around the cage (white circles), increasing density of the bone graft filler, and subchondral sclerotic changes (black thick arrows) over time.
3.2.3 Osseointegration of the cervical interbody cage

The sagittal plain film of 1 day after the surgery showed a small radiolucent line between the cage and the superior vertebral body (figure 10B). This radiolucent line gradually disappeared at 6 weeks post-surgery and was only present at the anterior half of the cage at 3 months post-surgery. No radiolucent band was noticed between the cage and the inferior vertebral body. Qualitative evaluation of the radiolucent line surrounding the cage was also possible on CBCT images (figure 11). Sagittal images at 1 day after the surgery demonstrated a small radiolucent line between the interface of the cage and the superior endplate. The radiolucent line disappeared at the images at 6 weeks and 3 months post-operatively. However, the coronal images indicated a small radiolucent line at the anterior side at the interface between the cage and the inferior vertebral body. This delineation between the cage and endplate became less clear over time.

Another qualitative observation on the CBCT images was the change in density of the bone graft filler (figure 11). The density of the bone graft filler gradually increased over the 3 time points. It was noted that the density did not increase equally over the entire area. It seemed that, on sagittal and coronal images, the outer layers of the bone graft filler had a higher density compared to the inner side of the bone graft filler.

A last qualitative observation was regarded as the sclerotic reaction at the subchondral bone of the vertebral bodies adjacent to the operated level. The coronal CBCT image of 6 weeks post-surgery showed a dense sclerotic bone change underlying the inferior endplate at the pressure areas of the cage wall (figure 11C). These subchondral sclerotic bone changes became more distinct at 3 months post-operatively.

3.2.4 Subsidence

On plain films, the anterior and posterior distance between the upper endplate of the superior vertebral body and the lower endplate of the inferior vertebral body was 38,2 and 35,9 mm, respectively, at 1 day post-surgery (figure 12). These measurements at 3 months post-surgery were 39,1 and 36,4 mm. Recalculation of the initial heights measured at the CBCT images at 1 day post-surgery, based on the magnification factor (26,2 mm at 1 day post-surgery and 27,3 at 3 months post-surgery) were 39,8 and 37,4 mm. This means that the height of the operated level was decreased with 0,7 mm anteriorly and with 1 mm at the posterior side at 3 months after the surgery. No subsidence of the cage into the vertebral bodies was demonstrated.
Figure 12: Measurement of subsidence on plain films following anterior cervical interbody fusion surgery at 1 day and 3 months post-surgery. The difference between the anterior and posterior height of the operated level (from upper endplate of the superior vertebral body to the lower endplate of the inferior vertebral body) at 1 day and 3 months of follow-up was measured. Taken the magnification factor into account, the difference was less than 2 mm, indicating no subsidence of the cage into the vertebral endplates.

Measurements on the CBCT images of 1 day and 3 months after the surgery determined a change in anterior height of the operated level of 32,0 mm to 31,7 and a change in posterior height of the operated level of 30,9 to 30,5 (figure 13). These findings illustrated a reduction of 0,3 and 0,4 mm in height of the operated level, meaning that no subsidence was shown at 3 months after the fusion surgery.

Figure 13: Measurement of subsidence on cone-beam CT images following anterior cervical interbody fusion surgery at 1 day and 3 months post-surgery. The difference between the anterior and posterior height of the operated level (from upper endplate of the superior vertebral body to the lower endplate of the inferior vertebral body) at 1 day and 3 months post-operatively was measured. The difference was less than 2 mm, indicating no subsidence of the cage into the vertebral endplates.
3.2.5 *Angular motion and translational motion*

The Cobb angle on the dynamic plain films at 3 months follow-up measured 5.4° on extension images and 4.8° of flexion images (figure 14). These measurements resulted in an angular motion of 0.6°, indicating no movement of the operated level, according to the Cobb angle. Translation on flexion and extension plain films of 3 months post-operatively is not visible. Therefore, it is concluded that no translational motion took place at 3 months follow-up.

![Figure 14: Measurement of the Cobb angle on flexion and extension plain films following anterior cervical interbody fusion surgery at 3 months post-surgery.](image)

3.2.6 *Clinical outcome*

Six weeks post-surgery, the VAS-score improved with 50% (from 6 to 3) for the neck pain and with 50% (from 8 to 4) for left arm pain. The NDI-score of the patient improved with 39% (from 46 to 28), compared to the initial condition before the surgery. The VAS- and NDI-scores improved further, with a total improvement of the VAS-score for neck pain with 67% (to 2) and for left arm pain with 63% (to 3), and the NDI-score of 57% (to 20) at 3 months follow-up. The patient had not suffered from right arm pain.
3.2.7 Comparison of radiation doses of CT and cone-beam CT for a scan of the cervical spine

The median CTDI-values for a scan of the cervical spine of the 4 CT devices and 1 CBCT device in our hospital were compared in order to calculate the difference in radiation doses. The median CTDI-values for the CT-scanners for scans of the cervical spine were 14,36, 17,24, 15,84 and 18,98. For the CBCT device, the median CTDI-value for a cervical spine scan was 7,94. When the different sizes of field of view were taken into account, these measurements revealed that the CT-scanners deliver a radiation dose that is between 3,62 and 4,78 times higher compared to the CBCT-scanner for scans of the cervical spine (figure 15).

**Figure 15:** Radiation dose represented by Computed Tomography Dose Index (CTDI)-values of the cone-beam CT (CBCT) device and 4 CT devices in this hospital. The median radiation dose of the CBCT device is almost 4 times lower (3,62-4,78) than the median radiation doses of the CT devices.

**CT 1:** Definition, Siemens; **CT 2:** Somatom Definition AS64 fast care, Siemens; **CT 3:** Somatom Emotion 6, Siemens; **CT 4:** Somatom Emotion 6, Siemens
3.2.8 Comparison of metal artefacts on cone-beam CT caused by different types of cervical interbody cages

Table 3: Cone-beam CT (CBCT) images showing metal artefacts caused by different types of cervical interbody implants after anterior cervical interbody fusion procedures. PEEK = Poly-Ether Ether Ketone

<table>
<thead>
<tr>
<th></th>
<th>CBCT sagittal view</th>
<th>CBCT axial view</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trabecular metal (tantalum)</strong> (Zimmer)</td>
<td><img src="https://via.placeholder.com/150" alt="Image" /></td>
<td><img src="https://via.placeholder.com/150" alt="Image" /></td>
</tr>
<tr>
<td><strong>PEEK + titanium coating</strong> (Cormed)</td>
<td><img src="https://via.placeholder.com/150" alt="Image" /></td>
<td><img src="https://via.placeholder.com/150" alt="Image" /></td>
</tr>
<tr>
<td><strong>Nanocrystalline hydroxyapatite</strong> (Pioneer)</td>
<td><img src="https://via.placeholder.com/150" alt="Image" /></td>
<td><img src="https://via.placeholder.com/150" alt="Image" /></td>
</tr>
<tr>
<td><strong>PEEK</strong> (Synthes)</td>
<td><img src="https://via.placeholder.com/150" alt="Image" /></td>
<td><img src="https://via.placeholder.com/150" alt="Image" /></td>
</tr>
</tbody>
</table>

Cages constructed of trabecular metal (tantalum) (Zimmer) showed various metal artefacts on CBCT images (table 3). The metal artefacts were demonstrated as broad band (streak) artefacts, represented as radiodense central artefacts and radiolucent lateral streak artefacts, which were running obliquely over the image. The metal artefacts impeded reliable evaluation of the bone fusion process between the endplates and cage/bone graft filler and the formation of trabecular bone outside the cage. However, the artefacts caused by tantalum on a CT-scan were radiodense over a bigger area compared to CBCT (table 4). The radiodense bands were also located posteriorly and anteriorly of the vertebrae on the CT-scan, whereas the artefacts in this area were less pronounced on CBCT images. On the CT-scan, the vertebral endplates of the operated vertebrae were completely invisible due to the radiodense artefacts.
PEEK cages with a titanium coating (Cormed) are radiolucent (table 3). However, several streak artefacts were shown, derived from the tantalum marker on the cage. The marker induced radiodense and radiolucent streak artefacts. These metal artefacts could impede the assessment of osseointegration of the cage and the bone fusion process. In addition, CBCT imaging demonstrated some metal streak artefacts caused by the anterior plate and screws and a radiolucent artefact next to the anterior plate. However, the radiolucent artefacts diminished rapidly with increasing distance from the anterior plate and did not involve the entire area necessary for bone evaluation.

Few metal artefacts were seen with cages composed of nanocrystalline hydroxyapatite (Pioneer), despite it is a radiopaque material (table 3). The radiodense cage caused a minimal of artefacts and did not affect the evaluation of the process of bone formation. Also in these images, the radiolucent metal artefact next to the anterior plate was noticed. Nanocrystalline hydroxyapatite also caused minimal artefacts on CT-scans (table 4). These minimal artefacts were, however, more pronounced than on CBCT-scans. It has to be noted that the CT-scan in the figure does not contain a metal anterior plate and screws.

Radiolucent PEEK cages from Synthes demonstrated minimal artefacts caused by the marker on the cage, which is composed of tantalum (table 3). The few artefacts caused by the tantalum marker were demonstrated as radiolucent artefacts around the marker, which diminished rapidly with increasing distance. In addition, the screws were composed of titanium and caused radiodense streak artefacts. The evaluation of the bone formation could be impeded, especially at the interface between the endplates and the cage/bone graft filler, because the screws are located in the proximity of the disc space in comparison to other applications where an anterior plate and screws is used.

**Table 4: Comparison of metal artefacts caused by different types of cages on cone-beam CT (CBCT) and CT after anterior cervical interbody fusion procedures.**

<table>
<thead>
<tr>
<th></th>
<th>CBCT</th>
<th>CT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trabecular metal</strong></td>
<td><img src="image1" alt="Image" /></td>
<td><img src="image2" alt="Image" /></td>
</tr>
<tr>
<td>(tantalum)</td>
<td><img src="image3" alt="Image" /></td>
<td><img src="image4" alt="Image" /></td>
</tr>
<tr>
<td>(<strong>Zimmer</strong>)</td>
<td><img src="image5" alt="Image" /></td>
<td><img src="image6" alt="Image" /></td>
</tr>
<tr>
<td><strong>Nanocrystalline</strong></td>
<td><img src="image7" alt="Image" /></td>
<td><img src="image8" alt="Image" /></td>
</tr>
<tr>
<td>hydroxyapatite</td>
<td><img src="image9" alt="Image" /></td>
<td><img src="image10" alt="Image" /></td>
</tr>
<tr>
<td>(<strong>Pioneer</strong>)</td>
<td><img src="image11" alt="Image" /></td>
<td><img src="image12" alt="Image" /></td>
</tr>
</tbody>
</table>
3.3 Clinical outcome of minimally invasive Discogel® injection

3.3.1 Clinical outcome

Table 5: The mean VAS-score, ODI-score, PCS and MCS of patients who received intradiscal Discogel® injection before the injection, 1 day, 3 weeks, 6 weeks and 3 months after the injection.

<table>
<thead>
<tr>
<th></th>
<th>Mean VAS-score</th>
<th>Mean ODI-score</th>
<th>Mean PCS</th>
<th>Mean MCS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Day 0</strong></td>
<td>5,8 ± 2,3</td>
<td>38 ± 11</td>
<td>32,3 ± 4,5</td>
<td>45,0 ± 12,9</td>
</tr>
<tr>
<td><strong>Day 1</strong></td>
<td>6,4 ± 2,0</td>
<td>51 ± 15</td>
<td>27,7 ± 7,8</td>
<td>50,0 ± 8,9</td>
</tr>
<tr>
<td><strong>Week 3</strong></td>
<td>4,3 ± 2,8</td>
<td>36 ± 20</td>
<td>36,4 ± 8,2</td>
<td>45,9 ± 13,2</td>
</tr>
<tr>
<td><strong>Week 6</strong></td>
<td>3,3 ± 2,8</td>
<td>27 ± 22</td>
<td>37,6 ± 10,3</td>
<td>53,0 ± 9,2</td>
</tr>
<tr>
<td><strong>Month 3</strong></td>
<td>3,4 ± 2,4</td>
<td>25 ± 19</td>
<td>38,9 ± 9,0</td>
<td>51,5 ± 11,6</td>
</tr>
<tr>
<td><strong>Improvement</strong></td>
<td>41%</td>
<td>34%</td>
<td>/</td>
<td>/</td>
</tr>
</tbody>
</table>

VAS = Visual-Analogue-Scale, ODI = Oswestry-Disability-Index, PCS = Physical Component Score, MCS = Mental Component Score

At baseline, the mean VAS-score of the patients was 5,8 (table 5 and figure 16). One day after the injection, the mean VAS-score increased to 6,4. A decrease in the VAS-score was noted at 3 weeks follow-up, followed by a further decrease at 6 weeks after the procedure. No further decrease was noticed 3 months after the injection. The mean VAS-score was improved with 41% at 3 months follow-up compared to the score before the injection. In 4 out of 8 patients the VAS-score was decreased with minimum 2 points or decreased to 0. Only 1 patient did not have an improved VAS-score at 3 months follow-up. However, this patient did experience an improvement in pain (73%) at 3 weeks after the injection. For the patients who experienced a decrease in the VAS-score, the decrease was noticed at 3 weeks to 6 weeks after the injection.

The same pattern was recognized for the mean ODI-score. The patients started with a mean ODI-score of 38 before the procedure, followed by an increase to 51 at 1 day after the procedure. Hereafter, the ODI-score decreased to 36 at 3 weeks after the procedure and to 27 at 6 weeks of follow-up. At 3 months after the procedure, the ODI-score (25) did not change from the score at 6 weeks follow-up. The ODI-score improved with 34% at 3 months follow-up compared to the baseline condition. The ODI-score was improved with more than 30% in 5 of the 8 patients. Two patients did not experience an improvement in functional ability at 3 months follow-up. For the patients who experienced an improvement in ODI-score, this improvement was noted after 3 to 6 weeks, as was also noted with the VAS-score improvement.

The PCS calculated from the SF-12 questionnaires also showed the same pattern as the VAS- and ODI-scores, but was relatively low. The mean PCS at baseline was 32,3. A decrease to 27,7 was observed at day 1, followed by an increase to 36,4 at 3 weeks, 37,6 at 6 weeks and 38,9 at 3 months follow-up. The mean MCS before the procedure was 45,0. The day after the injection, the MCS changes to 50,0, followed by 45,9 at 3 weeks follow-up, 53,0 at 6 weeks follow-up and 51,5 at 3 months follow-up.
Figure 16: Mean VAS-score, ODI-score, PCS and MCS of 8 patients who received intradiscal Discogel® injection worsened 1 day after the injection, but gradually improved at 3 weeks, 6 weeks and 3 months after the injection. VAS = Visual-Analogue-Scale, ODI = Oswestry-Disability-Index, PCS = Physical Component Score, MCS = Mental Component Score

Several patients left some questions blank in the questionnaires regarding patient satisfaction concerning the procedure. The questionnaires revealed that 6 patients were satisfied with the results of the procedure 3 months after the Discogel® injection, whereas zero patients were not satisfied (figure 17). Five patients indicated that their condition was better than before the injection, whereas the condition of 1 patient was the same as before the procedure at 3 months follow-up. Six patients would again undergo the procedure when they have discogenic pain and 6 patients would recommend Discogel® injection to a friend or family with discogenic pain.
Three months after the Discogel® injection, patients were satisfied with the results of the procedure, the condition of the majority patients was better than before the injection, the majority patients would undergo the procedure again and would recommend the procedure to a friend or family member.

### 3.3.2 Estimated economic effect

Discogel® injection has a cost of around 1300 to 1500 euros, whereas a single-level lumbar fusion surgery costs 5000 to 10000 euros, depending on the number of implanted cages and on complications. This results in a 80% lower cost compared to lumbar fusion surgery. The lower costs are mainly attributed to the hospital stay, pharmaceutical costs and surgeon fees. For a Discogel® injection, the patients stay in day clinic, whereas patients who underwent lumbar fusion surgeries stay for several days in the hospital. Additionally, a lumbar fusion surgery requires higher pharmaceutical costs because of the general anesthetics.

Furthermore, 3 months after the Discogel® injection, 5 out of 8 patients were back to work or normal sport activity. One patient started working again 6 months after the injection. The other 2 patients were not back to work due to remaining LBP.
4. Discussion

4.1 Early diagnosis of axial spondyloarthritis using MRI

In the past, diagnosis of axial SpA by medical imaging was performed using plain films or CT by showing chronic structural bone changes within the SIJ or to the spine. However, the early phase of axial SpA is not characterized by structural changes and is therefore not detectable on plain films or CT. MRI is the imaging modality of choice to detect active phases of axial SpA and is especially useful in patients with non-radiographic axial SpA. Therefore, MRI is nowadays the most frequently used imaging tool for the early diagnosis of axial SpA. A study by Rudwaleit et al. (30) demonstrated that among 649 patients who possibly had SpA, 60.2% were diagnosed with axial SpA based on MRI examinations according to the ASAS criteria. However, only 30% of all patients diagnosed with axial SpA had definite radiographic sacroilitis and fulfilled the modified New York criteria for AS on plain films. This outcome demonstrates the importance of MR imaging and the use of the ASAS criteria in diagnosing axial SpA, due to the capability of MRI to show active inflammation phases of SpA.

A correct, early diagnosis is important to select the most effective therapy for a particular patient in order to prevent the development of considerable pain and stiffness of the SIJ or the spine. Exercise therapy and NSAIDs are the backbone of medical treatments for axial SpA. When these treatments fail to improve the clinical symptoms, Tumor Necrosis Factor (TNF)-α-antagonists are considered as a therapy for axial SpA and these are most efficient in early stages of the disease, since remission rates of 50% have been demonstrated (39). Several conditions are required for repayment of anti-TNF-α medication. These conditions include the presence of chronic back pain for more than 3 months with an onset before the age of 45, ASAS positivity according to the imaging arm of the ASAS criteria (presence of sacroilitis and minimal 1 clinical feature of SpA), a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)\(^1\) of 4/10 or higher, an increased CRP-value, an insufficient response to previous use of minimal 2 NSAIDs and the absence of evolutionary tuberculosis. The importance of MRI examinations regarding these repayment conditions is illustrated in patients with non-radiographic SpA who subsequently have no evidence of sacroilitis on plain films, whereas the presence of active inflammation sites can be detected by MRI. This subset of SpA patients can experience the beneficial effect of MRI in early diagnosing SpA regarding the therapeutic decision and potential repayment of medication.

However, it is still arguable whether MRI evaluation of the SIJ is sufficient for the diagnosis of axial SpA or whether MRI evaluation of both SIJ and spine is necessary. The standard way, in this hospital, is to analyze only the SIJ. This study was performed in order to clarify whether imaging of the SIJ is sufficient to detect axial SpA or whether additional imaging of the spine is mandatory.

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1 BASDAI is a measurement describing disease activity of SpA
4.1.1 The ASAS criteria for detecting non-radiographic axial spondyloarthritis

The readers of this study evaluated the MR images according to the ASAS criteria in order to classify the images as positive or negative for active axial SpA. A high agreement (0.87%) between the two readers was demonstrated regarding the application of these criteria. However, there was some discussion, especially in the borderline cases. For these cases, the ASAS criteria are disputable.

The development of the ASAS criteria for axial SpA was an important step towards the diagnosis of the early stage of SpA and to detect new episodes of active inflammation in established axial SpA. However, several limitations show up in applying the ASAS criteria for diagnosing the disease. The first limitation is that the presence of structural changes to the SIJ or the spine are not sufficient to define sacroiliitis on MRI. However, chronic lesions are a sign that earlier inflammation has been present. A fused spine (bamboo spine) for example, is in the absence of bone marrow edema, not an indication for axial SpA according to the ASAS criteria. However, a bamboo spine is an established consequence of a non-treated osteitis patient. Also subchondral fat infiltration, visible as hyperintense spots on T1-weighted images, might indicate areas of previous inflammation. This is in contradiction with the modified New-York criteria because those are only based on structural changes visible on plain films. Secondly, the number and severity of the inflammatory lesions are not taken into account. A third limitation is that variation in the outcomes between different readers is almost always present, especially for borderline cases (5). Furthermore, it is important to recall that SpA is a fluctuating disease with periods of inflammation and with periods of remission. A negative MRI can thus not rule out SpA: it is possible that the MR image is taken during a remission period.

To conclude, the new ASAS criteria for axial SpA entail several limitations. Therefore, reassessment of these criteria would be beneficial. It is suggested that new criteria include the presence of structural changes and the number and severity of the inflammation lesions. A possible way to achieve this is by enabling more outcomes, such as ‘positive’, ‘probably positive’ and ‘negative’. Multiple outcomes would especially be useful in clinical practice, more than in scientific studies. Furthermore, new criteria should also take into account all the possible characteristics of axial SpA: the radiological outcome, the clinical symptoms and the laboratory findings (HLA-B27 and CRP).

4.1.2 MRI examination of the sacroiliac joints alone or both sacroiliac joints and spine

Disagreement exists in whether imaging of the SIJ alone is sufficient for a reliable diagnosis of axial SpA, because in some patients, only the spine is affected with active inflammation. This study investigated the number of SpA patients when diagnosis was based on evaluation of SIJ MR images alone and evaluation of both SIJ and spine MR images. All data of our study (86 images) could not be considered as independent because multiple MRI examinations were derived from the same patient. Therefore, the data were analyzed as one outcome for SIJ MRI evaluation and one outcome for spine MRI evaluation for each patient. Reader 1 and 2, respectively assessed 11 and 14 of 32 patients with active inflammation. Combined assessment of SIJ and spine MR images increased these numbers to 15 and 18. This means that 4 patients (12,5%) with a negative SIJ MRI were classified as active SpA based on the inflammation detected on the spine MRI. This study in this limited group
of patients demonstrated no significant difference between the numbers of patients in both groups. Based on the results of this study, it can be concluded that MR imaging of the spine is not advised in addition to MR imaging of the SIJ in order to diagnose active axial SpA. However, a substantial number of patients (12.5%) will be overlooked if only the SIJ is evaluated. An additional MRI examination of the spine in all patients who were suspected to have axial SpA requires extra costs and longer scanning times. Therefore, it could be recommended that a spine MRI in addition to the SIJ MRI is only recommended in patients who complain from excessive, long lasting back pain.

An important remark that has to be mentioned is that a part of the lumbar spine is visible on the MR images of the SIJ. This signifies that evaluation of the lower lumbar bodies is possible on SIJ MR images. One of the 4 patients who were ASAS positive for the spine MRI and negative for the SIJ MRI, had 2 lesions on L5 and 1 lesion on S1, making the spine positive according to the ASAS criteria. However, these lesions were also visible on the SIJ MRI. The additional spine MRI evaluation did not have an incremental contribution to the diagnosis for this patient.

Power analysis of this study revealed, with an alpha confidence level of 0.05, that the power of this study was 44%. This means that the probability to detect a significant difference, when there is a significant difference, is only 44%. The finding that there is no statistical significant difference between the numbers of SpA patients of both groups, can be due to the low power of this study. Nevertheless, the power of this study could be elevated by increasing the number of patients in this study. However, this was not possible for this retrospective study. Sample size calculations for a chi-square test with proportions similar to the results of this study (34.4% for SIJ MRI examination alone and 46.9% for both SIJ and spine MRI examination) revealed that the required number of subjects is around 100 patients in order to detect significant differences with a power of 0.80 (alpha confidence level of 0.05).

An extensive study by Weber et al. (40) assessed the incremental diagnostic value of spine MRI evaluated in combination with SIJ MRI in non-radiographic axial SpA patients and compared this with SIJ MRI alone. The study was performed in 2 independent cohorts. The results demonstrated that 15.8% and 24.2% (in the 2 cohorts) of patients who had a negative SIJ MRI, were reclassified as positive for axial SpA by evaluation of both SIJ and spine MRI. However, 26.8% and 11.4% of non-specific back pain controls and healthy volunteers with negative SIJ MRI were falsely reclassified as positive for axial SpA by evaluation of both SIJ and spine MRI. The authors of this study concluded that combined evaluation of SIJ and spine MRI added little incremental value compared with SIJ MRI alone for diagnosing patients with non-radiographic axial SpA. Vertebral corner lesions on spine MRI were the main drivers for misclassification of healthy controls.

To conclude, additional MR imaging of the spine in combination with the SIJ is not recommended according to the results of this study (figure 18). However, in this study, 12.5% of patients would only be diagnosed with active axial SpA if the spine MRI was investigated in combination with the SIJ MRI. Because of this substantial number, it can now be advised, considering the extra costs and scanning time, to take the additional spine MRI only in patients with specific and long lasting back pain complaints. However, the results of this study with a limited number of patients need to be
confirmed in larger patient cohorts and additional research is necessary with regard to the spinal corner lesions and whether these are sensitive features of axial SpA.

4.2 Cone-beam CT for the radiological follow-up of cervical fusion surgeries

4.2.1 Radiological guidelines for post-operative evaluation of spinal fusion

The radiologist’s task is to investigate whether the fusion is successful, ongoing or whether a pseudarthrosis is formed. A successful fusion is characterized by continuous trabecular bone bridging and no mobility of the operated level. Signs of ongoing fusion are the appearance of hazy densities in the disc space around the cage, subsequent formation of a trabecular bone bridge, the disappearance of a radiolucent line at the interface between vertebral endplates and the cage, a minimal loss of disc height, good integrity of the surgical material (cage, anterior plate and screws) and angular and translational immobility (41). The hazy densities which can be observed in the disc space around the case represent matrix calcification and thus ongoing bone formation. The change of the radiolucent line into a more radiodense area over the different time points represents bony integration of the bone graft filler with the vertebral body. Translational immobility is assumed when there is no displacement of one vertebral body to the adjacent vertebral body in anteroposterior direction.

Signs of ongoing pseudarthrosis are a sharp delineation of the bone formation by sclerotic borders instead of a continuous trabecular bone bridge, the persistence of the radiolucent line between the cage and the vertebral endplates, fractured or loosening of the anterior plate or screws, a change in position of the cage, subsidence of the cage into the vertebral endplates and sclerotic change in the adjacent vertebrae (41). Fractured or loose anterior plate or screws diminish vertebral stability, and are therefore often indications of vertebral mobility and this can impede a successful fusion formation. Subsidence is regarded as a shift of the cage into the vertebral endplate located superior and/or inferior of the cage. Subsidence is assumed when the intervertebral disc height is reduced with more than 2 mm. However, subsidence does not always mean pseudarthrosis: a successful fusion is possible when subsidence of the cage into the vertebral bodies is noted. However, the reduced disc height can result in impingement on spinal nerve roots. A last indication which is sometimes a sign of pseudarthrosis is bone sclerosis. This is a reaction of the vertebrae due to the implantation of the cage. The cage performs a pressure on the endplates of the adjacent vertebrae. The vertebrae react by producing a dense, more robust bone in the vicinity of the pressure points of the cage.

The radiologist needs to evaluate all these items in order to define whether a successful fusion, ongoing fusion or pseudarthrosis took place. The last item which must be evaluated is a frequently observed consequence of a successful fusion: adjacent disc degeneration. The fixation of two or more vertebrae increases the pressure on the adjacent disc levels which increases the rate at which those levels degenerate (21).
The process of bony fusion is generally monitored by interpretation of the bony changes which are visible on plain films. Plain films are the mainstay for post-operative follow-up of spinal fusion surgeries because of its low costs and the relative safety for the patient. In order to define a successful fusion on plain films, the FDA criteria need to be achieved: evidence of trabecular bone bridging, an angular motion of less than 5° and a translational motion of less than 3mm (26).

Most of the features which need to be evaluated are well evaluable on plain films, in particular vertebral mobility by measuring the Cobb angle and translational motion on flexion and extension views. However, evaluation of beginning bone formation, the radiolucent line and sclerotic reactions of the vertebral endplates is often impeded on plain films because of superposition.

4.2.2 Cone-beam CT in order to assess bony fusion following cervical fusion surgery

CBCT enables cross-sectional imaging of the cervical spine in the presence of metal implants, thereby maintaining a high resolution and a relatively low radiation dose. In this case study, CBCT was successfully described as a novel imaging technique for the post-operative evaluation of ACIF procedures in a patient implanted with a Cormed TSC cage and subsequent stabilization with an anterior plate with screws. However, CBCT is only useful for the follow-up of spinal surgeries in the cervical spine due to the limited size of the CBCT bore.

The cross-sectional characteristic of CBCT imaging enabled visualization of the ongoing bone fusion process in the disc space around the cage, visualization of the bone graft filler inside the cage and the evaluation of the presence or absence of a radiolucent line between the bone graft filler and the vertebral endplates. In addition, ongoing bony fusion was demonstrated by bone apposition to the vertebral endplates, followed by the appearance of hazy densities. In later stages, the formation of a continuous trabecular bone bridge would probably take place (supplemental information S3 2). The sagittal CBCT image of 6 weeks follow-up showed the presence of hazy densities in the disc space around the cage, which could represent matrix mineralization. These hazy densities were still present at 3 months post-surgery. However, it is questionable whether these densities represent matrix calcification, a part of the ongoing fusion process, or whether they are caused by metal artefacts. Nevertheless, the hazy densities are also present on axial images. Therefore, it can be concluded that the densities indicate matrix calcification, and thus ongoing fusion. Axial images are useful to assess the amount of bony changes. Furthermore, disappearance of the radiolucent line around the cage was noted. In addition, the observed increase in density of the bone graft filler signifies calcification of the bone graft filler. The finding that the density of the outer layers of the bone graft filler has increased more than the density of the bone graft filler in the middle, could indicate the beneficial effect of the titanium coating of the Cormed TSC cages in osseointegration of the cage into the vertebral bodies. Such a detailed demonstration of the bone fusion process following ACIF procedures (particularly the presence of hazy densities representing bone matrix calcification) is not possible with standard imaging, such as plain films and classical CT-scanning.

CBCT could be a potential medical imaging technique to evaluate the bone fusion process following ACIF surgeries due to its high spatial resolution, lower radiation dose and reduction in artefacts.
caused by metal implants in comparison to conventional CT. In general, new CBCT devices reach a higher spatial resolution than CT devices, namely up to 100 µm or less (34). As the results of this study demonstrate, CBCT-scanning has an approximately 4 times lower radiation dose compared to classical CT-scanning for the patient in our hospital. A study by Loubele et al. (35) has found that the effective radiation dose of CBCT for dental and maxillofacial applications ranged from 12 to 82 µSv, whereas the corresponding values for CT ranged from 474 to 1160 µSv. A reduction in radiation exposure for the patient is beneficial, considering the number of scans the patient needs to undergo from before the diagnosis until the end of the follow-up period. In addition, it is important to adhere to the ALARA (as low as reasonably achievable) principle, not only for the patient but also for the clinicians.

Another advantage of using CBCT for the follow-up of ACIF procedures is the reduction in the amount of metal artefacts compared to classical CT. The cage, markers on the cage, anterior plate and the screws are often constructed of metal and interfere with the image quality of the scan. In some cases, metal artefacts can be reduced or even avoided by adjusting the scanning parameters, such as the field of view, the scanning time, the slice width, tube potential and tube current (37). The artefacts are demonstrated as radiodense or radiolucent streak artefacts. However, they are less abundant on CBCT images compared to CT images. Sometimes the artefacts affect the area in which the fusion process takes place, which can hinder the assessment of the bone fusion status. However, the artefacts diminish rapidly with increasing distance from the implant and does not affect the total scan. By comparing the metal artefacts caused by different types of cages used in the hospital, it is noted that some materials cause less artefacts than others. Trabecular metal (tantalum), which is used to construct the cages of Zimmer, causes relative many streak artefacts. The markers of the cages of Cormed and Synthes are also constructed of tantalum. These smaller pieces of tantalum cause some small artefacts in the proximity of the marker and can sometimes affect the evaluation area. The titanium plates and screws cause a lot of streak artefacts, mostly outside the area of bone formation assessment. Almost no artefacts are caused by nanocrystalline hydroxyapatite cages (Pioneer). Nanocrystalline hydroxyapatite looks a useful radiopaque material which does not affect the image quality and the subsequent ability to evaluate the ongoing bone fusion process. Metal streak artefacts are caused by multiple mechanisms, such as beam hardening and scatter effects. The dark streaks between metal (and bone), surrounded by bright streaks, are a result of the beam hardening and scatter. Beam hardening is the result of the attenuation of X-rays with low energy as the X-rays flow through the tissue, resulting in an X-ray beam with a higher average energy than the initial beam. Scatter effects are caused when the photons in an X-ray beam reach a specific tissue followed by a change in their direction. These photons will then end up in a different detector (42).

In summary, CBCT-scanning provides the ability to evaluate the general bony fusion process, except for the Cobb angle (angular motion) and translational motion. Evaluation of the mobility of the operated level still requires plain films, due to its possibility to obtain flexion and extension images. Therefore, CBCT, instead of classical CT, can be used besides plain films in order to supplement the shortcomings of plain films in evaluating the bone fusion process. For the patient in this case,
immobility of the operated level was demonstrated by the angular and translational motion. However, a continuous trabecular bone bridge was not yet demonstrated. The disappearance of the radiolucent line at the interface between the cage and the adjacent vertebral bodies, the absence of subsidence and the increase in bone graft filler density are features which suggest ongoing fusion (figure 18).

4.3 Clinical outcome of minimally invasive Discogel® injection

Intradiscal injection of Discogel® has been proposed as a potential minimally invasive treatment option for chronic discogenic LBP in clinical trials (22, 43, 44). The current study reported the clinical outcome of Discogel® injection in 8 young active patients with PMBD who showed no response to non-operative treatments and who met the criteria for lumbar interbody fusion surgery. The results of this proof of concept study demonstrated that Discogel® injection seems a promising minimally invasive treatment for young active patients with PMBD. Most patients experienced an improvement in pain intensity and functional ability already after 3 to 6 weeks. At 3 months after the procedure, the average pain intensity was improved with 41% and functional ability was improved with 34%. The physical and mental health in the patients’ point of view was slightly increased. However, the PCS was still lower than 50. A PCS and MCS of 50 is regarded as ‘average’ in the general population. A lower score indicates a worse physical or mental condition in the patients’ point of view, whereas a higher score indicates a better condition. In this limited number of patients, Discogel® injection was effective in postponing a fusion surgery.

It is important to take into account that the patients who were considered for a Discogel® injection were selected carefully. The patients were young, active and had a damaged dehydrated disc, appearing black on MRI, preferably single-level.

Our study showed similar results as found in the literature. A study by Volpentesta et al. (22) demonstrated in a prospective randomized study that percutaneous injection of Discogel® treatment had a successful result in 90% of the cases compared to 69% of control patients who received injections of a steroid and anesthetic at 3 months of follow-up. 89% of these Discogel® patients experienced LBP improvement on the day of the procedure or on the day after. LBP improvement had a delay of 7-10 days in 11% of the patients. This finding is different with the results of our study, where the patients experienced an increase in pain intensity the day after the procedure, followed by a strong decrease 3 to 6 weeks after the injection. Another prospective study by de Sèze et al. (43) with 79 patients showed that 75% of patients who received a Discogel® injection were judged to have good or very good results. Discogel® injection in combination with a local corticoid showed an overall success rate of 89%, as demonstrated by Theron et al. (44).

The exact pathology of discogenic LBP is still not completely understood. A study by Peng et al. (45) found that the discs from patients with discogenic LBP contained a zone of vascularized granulation tissue with extensive innervation in fissures extending from the outer part of the annulus into the nucleus pulposus. In this zone of the vascularized granulation tissue, abundant nociceptive nerve fibers were demonstrated. The increase in intradiscal pressure as a result of the injection of contrast
medium during a discography procedure, produces an irritation of those nociceptive nerve fibers and corresponding pain.

Discogel® is a viscous mixed solution of ethanol, cellulose derivative product and a radiopaque element, tungsten. Ethanol is the active component of Discogel® and it is a well-known solution having a necrotizing effect on biological tissues (46). Ethyl cellulose is added in order to create a more viscous solution because pure ethanol would readily diffuse into the surrounding tissues resulting in radicular burning pain (46). Discogel® also consists of tungsten, a radiopaque solution, enabling the visualization of the injected Discogel® on fluoroscopy during the injection. The exact working mechanism of Discogel® is not completely understood. However, 2 hypotheses could explain the effectiveness of intradiscal Discogel® administration. The first hypothesis is based on reducing the intradiscal pressure by the following mechanism. Inside the disc, ethanol produces a degradation of proteoglycans and glycosaminoglycans present in the nucleus pulposus. Degradation of these molecules decreases their water-retaining capacity and subsequently leads to dehydration of the turgid and protruding disc. This mechanism results in early pain, followed by a decrease in pain intensity (44, 46). The rational underlying the second hypothesis is the necrotizing effect of ethanol. This hypothesis is founded by damaging of the nociceptors present in the nerve fibers of the annulus fibrosus, as an increase in nerve fibers is found in damaged discs (46).

Other minimally invasive procedures regarding the intradiscal injection of a substance have already been proposed. Chymopapain is derived from the papaya fruit and found its use in treating discogenic pain. Chymopapain works by depolymerizing proteoglycans and glycoproteins inside the nucleus pulposus, and subsequent reduction in water retention. This results in shrinkage of the bulging disc. Chymopapain was approved by the United States FDA in 1982 and has been used for more than 30 years. However, several complications were reported as a result of the intradiscal injection of this solution. The most important complication was anaphylaxis, reported in 1% of the cases. Many controversy was reported about the use of chymopapain for a treatment for discogenic pain due to the many complications and it was therefore withdrawn from the market (2).

Furthermore, Peng et al. (47) studied the intradiscal administration of methylene blue in 36 patients (and 35 patients who received a placebo treatment) as a treatment option for patients with chronic discogenic LBP who were unresponsive to conservative therapy and who met the criteria for lumbar interbody fusion surgery. This study was a randomized double-blind placebo-controlled trial. Six months after the injection, the patients in the methylene blue group showed a mean pain reduction of 47.39 as measured by the Numeric-Rating-Scale (NRS)-score (a 101-point scale to assess pain) and a mean reduction in ODI-score of 32.47. However, the mean improvement of the NRS-score in the placebo group was 3.77 and the ODI-score improved by a mean of 0.97. This study indicated a favorable outcome as a result of intradiscal methylene blue administration. The postulated mechanism of action of methylene blue is denervation of small nociceptive fibers present in the annulus fibrosus (48). However, a previous study in our hospital investigating the clinical effect of methylene blue administration in patients with discogenic LBP did not demonstrate a significant clinical effect compared to the placebo group. This could be due to the low number of subjects (11
patients in methylene blue group and 13 patients in the placebo group) and a short follow-up of only 1 month. For this reason, our study was set up in an attempt to demonstrate a positive effect on clinical outcome after intradiscal injection of Discogel® in patients with discogenic LBP.

Economically, intradiscal injection of Discogel® as an alternative, less invasive treatment for patients with PMBD, has beneficial effects compared to lumbar interbody fusion surgeries. Firstly, Discogel® injection is much cheaper compared to fusion surgery, because it requires a shorter hospital stay, lower pharmaceutic costs and a lower cost for surgeon fees. Secondly, due to the minimally invasive feature of intradiscal Discogel® injection, a high return to work is noted.

To conclude, the results of this study with a limited number of patients demonstrated that intradiscal injection of Discogel® looks a promising minimally invasive technique to treat young active patients with PMBD (figure 18). Discogel® injection is an intermediate technique between conservative therapy and fusion surgery and could therefore postpone a lumbar interbody fusion surgery. In addition, it is associated with a high return to work and is a lot cheaper than surgery. However, further research is necessary to confirm these results in a larger patient cohort and with a longer follow-up period, and possibly with a control (placebo) group.
Conclusion

Based on the results of this study, it can be concluded that MRI evaluation of the spine in addition to MRI evaluation of the SIJ is not recommended for the early diagnosis of active axial SpA. However, a substantial (not significant) amount of patients will be overlooked if spinal inflammatory lesions were not investigated. Therefore, it can be advised to perform an additional MRI in a subset of patients with specific and long-lasting back pain. However, these results need to be confirmed in a larger patient cohort. Secondly, a different type of conventional CT, CBCT, was successfully described as a novel and useful imaging technique for the assessment of the bone fusion status following ACIF surgeries in this pilot study. The most important strengths of CBCT in comparison to other imaging techniques are the cross-sectional imaging, high spatial resolution, relative low radiation dose and few metal artefacts. In addition, image-guided intradiscal injection of Discogel® improved the pain and functional ability of patients with PMBD who were candidates for a lumbar interbody fusion surgery, at 3 months after the injection. This minimally invasive treatment with Discogel® could postpone an intervertebral fusion surgery. Further investigations should focus on the long-term clinical outcome in larger patient cohorts (figure 18).

These 3 clinical situations demonstrate that advanced radiological techniques are effective in precise assessment of the spinal fusion process or to postpone surgical fusion. This was demonstrated using following radiological techniques: MRI for the early diagnosis of active SpA, CBCT for the follow-up of intervertebral fusion surgeries and image-guided intradiscal injection of Discogel® in order to reduce the discogenic pain and to postpone a fusion surgery.
### Research question 1: comparative study
Do we need MRI of the SIJ alone or MRI of both SIJ and spine for a reliable diagnosis?

<table>
<thead>
<tr>
<th>Patients</th>
<th>MRI of SIJ and spine</th>
<th>Evaluation</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>32</td>
<td>MRI of SIJ and spine</td>
<td>Evaluation according to the ASAS criteria</td>
<td>Additional spine MRI was not indicated for diagnosis of active SpA.</td>
</tr>
</tbody>
</table>

### Research question 2: pilot study
Is CBCT a useful imaging technique to describe the ongoing fusion process post ACIF?

<table>
<thead>
<tr>
<th>Patients</th>
<th>MRI of SIJ and spine</th>
<th>Evaluation</th>
<th>Conclusion</th>
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<tr>
<td>1</td>
<td>Serial CBCT-scans over 1 year</td>
<td>Qualitative analysis of serial CBCT images</td>
<td>CBCT was successfully used as a novel imaging technique to assess bony fusion following ACIF.</td>
</tr>
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</table>

### Research question 3: clinical outcome study
What is the clinical outcome of patients at 3 months after Discogel® injection?

<table>
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<tr>
<th>Patients</th>
<th>MRI of SIJ and spine</th>
<th>Evaluation</th>
<th>Conclusion</th>
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<tr>
<td>8</td>
<td>Intradiscal injection and clinical follow-up</td>
<td>Analysis of questionnaires (VAS- and ODI-scores)</td>
<td>Discogel® injection improved patients’ pain and functional ability, thereby postponing fusion surgery.</td>
</tr>
</tbody>
</table>

### Case report:
'Tijdschrift voor Geneeskunde'
(Supplemental information S3 1)

### Abstract and Poster:
'Belgian Society of Neurosurgery'
(Supplemental information S3 4)

![Figure 18: Overview of the research questions, subjects, methods and conclusions of the 3 studies described in this report and corresponding scientific output during the internship.](image-url)
References


36. QRsrl, Verona-Italy. NewTom Cone Beam 3D Imaging, 5G.


46. Instruction manual DiscoGel(R). Notice Version 14/05/2013.


Supplemental information

1. Figures

**S1 1: Procedure of Discogel® injection.** Pre-operative diagnostic T2-weighted MR image showing black disc and annulus fibrosus tear (white arrow) (A). Fluoroscopic image of the Discogel® injection during the procedure (B). CT-scan after the procedure demonstrating the Discogel® in the nucleus pulposus extending into the annulus tear (C).

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**Modified New York criteria (1984)**

<table>
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<tr>
<th>1 radiographic criterion</th>
<th>AND</th>
<th>≥ 1 clinical criterion</th>
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<tr>
<td>Bilateral sacroiliitis grade 2 to 4</td>
<td>- Low back pain for ≥ 3 months improved by exercise and not relieved by rest</td>
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<tr>
<td>Unilateral sacroiliitis grade 3 or 4</td>
<td>- Limitation of lumbar spine motion in sagittal and frontal planes</td>
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Grade 0: Normal  
Grade 1: Suspicious changes  
Grade 2: Sclerosis, some erosions  
Grade 3: Severe erosions, widening/ narrowing of the joint space, some ankylosis  
Grade 4: Total ankylosis

**S1 2: Diagnosis of axial spondyloarthritis (SpA) according to the Modified New York criteria (1984).**
The modified New York criteria were developed for diagnosis of SpA on plain films. Diagnosis requires 1 radiographic criterion (bilateral sacroiliitis of minimal grade 2 or unilateral sacroiliitis of minimal grade 3) and minimal 1 clinical criterion.
S1 3: Anteroposterior plain film of a "bamboo spine". (from A. Vlajkovi, C. Schueller-Weidekamm; Spondylarthropathy; European Society of Musculoskeletal Radiologie (ESSR) 2014)
2. Questionnaires

S2 1: Dutch version of Visual Analogue Scale (VAS)-score for follow-up of anterior cervical interbody fusion surgery (ACIF) procedure.

Gelezen deze vragenlijst in te vullen. Deze is opgesteld om informatie in te winnen over uw lage rug pijn, de pijn in uw linker been en de pijn in uw rechter been. Voor de antwoorden op de vragen is er een schaal voorhanden, in de vorm van vakjes. Gelezen ELKE VRAAG te beantwoorden door EXACT EÉN VAKJE aan te duiden, het vakje dat het best uw persoonlijke situatie beschrijft OP DIT MOMENT. Het meest linkse vakje stelt het meest negatieve antwoord voor, het uiterste rechterse vak het meest positieve.

Nek Pijn
Op een schaal van 0 tot 10, gelieve de INTENSITEIT van uw nek pijn aan te geven met “0” indien u geen pijn hebt en met “10” indien uw pijn het ergste is dat u zich kan inbeelden.

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| Pijn is het ergste dat u zich kan inbeelden

Op een schaal van 0 tot 10, gelieve aan te duiden HOE VAAK U Pijn ondervindt van uw nek met “0” indien u er nooit pijn van ondervindt en met “10” indien u er altijd pijn van ondervindt.

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Linker Arm Pijn
Op een schaal van 0 tot 10, gelieve de INTENSITEIT van uw linker arm pijn aan te geven met “0” indien u geen pijn hebt en met “10” indien uw pijn het ergste is dat u zich kan inbeelden.

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| Pijn is het ergste dat u zich kan inbeelden

Op een schaal van 0 tot 10, gelieve aan te duiden HOE VAAK U Pijn ondervindt van uw linker arm met “0” indien u er nooit pijn van ondervindt en met “10” indien u er altijd pijn van ondervindt.

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Rechter Arm Pijn
Op een schaal van 0 tot 10, gelieve de INTENSITEIT van uw rechter arm pijn aan te geven met “0” indien u geen pijn hebt en met “10” indien uw pijn het ergste is dat u zich kan inbeelden.

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| Pijn is het ergste dat u zich kan inbeelden

Op een schaal van 0 tot 10, gelieve aan te duiden HOE VAAK U Pijn ondervindt van uw rechter arm met “0” indien u er nooit pijn van ondervindt en met “10” indien u er altijd pijn van ondervindt.

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Werk- en Sport Activiteiten
In vergelijking met uw situatie alvorens dat de pijn begon, in welke mate zijn uw activiteiten veranderd?

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<th>Werk Activiteiten:</th>
<th>Zelfde werk</th>
<th>Lagere werk activiteit</th>
<th>Werk gestopt</th>
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<tr>
<td>Sport Activiteiten:</td>
<td>Zelfde sport(e)</td>
<td>Lagere sport activiteit</td>
<td>Sporten gestopt</td>
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S2 2: Dutch version of Neck-Disability-Index (NDI) questionnaire for follow-up of anterior cervical interbody fusion (ACIF) procedure.

Gelieve deze vragenlijst in te vullen. Deze is opgesteld om te evalueren hoe uw rugproblemen uw capaciteiten beïnvloeden om uw dagelijkse activiteiten uit te voeren. Beantwoord elk onderdeel. Geef IN ELK INDERDEEL EÉN enkel antwoord, namelijk het antwoord dat het beste uw staat OP DIE DAG beschrijft.

Onderdeel 1 - Intensiteit van de Pijn
- Op dit moment voel ik helemaal geen pijn.
- Op dit moment voel ik een heel lichte pijn.
- Op dit moment voel ik een matige pijn.
- Op dit moment voel ik een tamelijk intense pijn.
- Op dit moment voel ik een zeer intense pijn.
- Op dit moment is de pijn onvoorstelbaar intens.

Onderdeel 2 - Persoonlijke Verzorging
- Ik kan mijn dagelijkse verzorging normaal uitvoeren, zonder dat dit extra pijn oplevert.
- Ik kan mijn dagelijkse verzorging normaal uitvoeren, maar dit is zeer pijnlijk.
- Ik moet mijn dagelijkse verzorging voorzichtig en langzaam uitvoeren, en ik voel daarbij pijn.
- Ik heb hulp nodig voor mijn dagelijkse verzorging, maar ik kan het grootste gedeelte ervan nog zelf uitvoeren.
- Ik heb elke dag hulp nodig voor het grootste gedeelte van mijn persoonlijke verzorging.
- Ik kan mij niet meer aankleden, ik was mij moeizaam en blijf in bed.

Onderdeel 3 - Dragen van Lasten
- Ik kan lasten optillen zonder dat dat de pijn verergert.
- Ik kan zware lasten optillen, maar daardoor vererger de pijn.
- Ik kan door de pijn geen zware lasten van de grond tillen, maar ik kan dat wel als ze op een hogere plaats staan (bijvoorbeeld op een tafel).
- Ik kan door de pijn geen zware lasten tillen, maar ik kan lichte tot matige zware lasten tillen als ze op een geschikte plaats staan.
- Ik kan alleen zeer lichte lasten optillen.
- Ik kan niets tillen of dragen.

Onderdeel 4 - Lezen
- Ik kan zoveel lezen als ik wil, zonder pijn in mijn nek.
- Ik kan zoveel lezen als ik wil, met heel lichte pijn in mijn nek.
- Ik kan zoveel lezen als ik wil, met matige pijn in mijn nek.
- Ik kan niet zoveel lezen als ik wil omwille van matige pijn in mijn nek.
- Ik kan bijna niet lezen omwille van ernstige pijn in mijn nek.
- Ik kan helemaal niet lezen.
Onderdeel 5 - Hoofdpijn

☐ Ik heb helemaal geen hoofdpijn
☐ Ik heb heel lichte hoofdpijn op onregelmatige momenten.
☐ Ik heb matige hoofdpijn op onregelmatige momenten.
☐ Ik heb matige hoofdpijn op regelmatige momenten.
☐ Ik heb ernstige hoofdpijn op regelmatige momenten.
☐ Ik heb bijna de gehele tijd hoofdpijn.

Onderdeel 6 - Concentratie

☐ Ik kan me volledig concentreren, wanneer ik wil en zonder moeite.
☐ Ik kan me volledig concentreren, wanneer ik wil, met heel lichte moeite.
☐ Ik heb redelijk wat moeite om me, wanneer ik wil, te concentreren.
☐ Ik heb heel veel moeite om me, wanneer ik wil, te concentreren.
☐ Ik heb zeer veel moeite om me, wanneer ik wil, te concentreren.
☐ Ik kan me helemaal niet concentreren.

Onderdeel 7 - Werk

☐ Ik kan zo veel werken als ik wil.
☐ Ik kan enkel mijn normaal werk doen, maar niet meer.
☐ Ik kan het meeste van mijn normaal werk doen, maar niet meer.
☐ Ik kan mijn normaal werk niet meer doen.
☐ Ik kan bijna geen werk meer doen.
☐ Ik kan helemaal niet meer werken.

Onderdeel 8 - Rijden

☐ Ik kan auto rijden zonder nek pijn.
☐ Ik kan auto rijden, zo lang als ik wil, met heel lichte nek pijn.
☐ Ik kan auto rijden, zolang als ik wil, met matige nek pijn.
☐ Ik kan niet zolang als ik wil auto rijden, omwille van matige nek pijn.
☐ Ik kan bijna niet auto rijden omwille van ernstige nek pijn.
☐ Ik kan helemaal niet auto rijden.
### Onderdeel 9 - Slapen

- Ik heb geen last om te slapen.
- Mijn slaap is heel licht verstoord (minder dan 1 uur slapeloos)
- Mijn slaap is licht verstoord (1 tot 2 uur slapeloos)
- Mijn slaap is matig verstoord (2 tot 3 uur slapeloos)
- Mijn slaap is ernstig verstoord (3 tot 5 uur slapeloos)
- Mijn slaap is volledig verstoord (5 tot 7 uur slapeloos)

### Onderdeel 10 - Ontspanning

- Ik kan al mijn ontspanningsactiviteiten doen zonder nek pijn.
- Ik kan al mijn ontspanningsactiviteiten doen, met lichte nek pijn.
- Ik kan de meeste, maar niet alle, van mijn ontspanningsactiviteiten doen (omwille van nek pijn)
- Ik kan slechts enkele van mijn ontspanningsactiviteiten doen (omwille van nek pijn)
- Ik kan bijna geen ontspanningsactiviteiten doen omwille van nek pijn.
- Ik kan helemaal geen ontspanningsactiviteiten doen.

---

**S2 3: Dutch version of Visual Analogue Scale (VAS)-score for Discogel® injection.**

**Rugpijn:**

Gelieve een verticale streep te zetten ( | ) dwars door onderstaande lijn die de mate van rugpijn aangeeft die u, gedurende de afgelopen week, voelde wanneer u actief was (bijv. wandelen, de trap nemen, huishoudelijk werk, in rusttoestand).

<table>
<thead>
<tr>
<th>Geen pijn</th>
<th>Ergst mogelijke pijn</th>
</tr>
</thead>
</table>
**S2 4: Dutch version of Oswestry Disability Index (ODI)-score for Discogel® injection.**

Deze vragenlijst is gemaakt om ons informatie te geven over uw rug. We kunnen hiermee nagaan hoe uw rugpijn u belemmert tijdens dagelijkse werkzaamheden. Beantwoordt u alstublieft ieder onderdeel. Kruis bij ieder onderdeel het bolletje aan dat best op u van toepassing is. Soms is het moeilijk om tussen twee antwoorden te kiezen, kruis dan het bolletje aan dat uw probleem het beste beschrijft.

### Onderdeel 1: Ernst van de pijn
- Ik heb geen pijn op dit moment
- De pijn is heel mild op dit moment
- De pijn is matig op dit moment
- De pijn is nooit hevig op dit moment
- De pijn is erg hevig op dit moment
- De pijn is het ergst denkbaar op dit moment

### Onderdeel 2: Zelfverzorging (wassen, kleden, enz.)
- Ik kan mijzelf normaal wassen en aankleden zonder extra pijn
- Ik kan mijzelf normaal wassen en aankleden maar heb dan wel extra pijn
- Als ik mijzelf was en aankleed doet het pijn en daarom ben ik daar langzaam en voorzichtig mee
- Ik heb enige hulp nodig maar kan m.b.t. wassen en aankleden het meeste zelf doen
- Ik heb elke dag hulp nodig bij de meeste aspecten van de zelfverzorging
- Ik kleed me niet aan, was mezelf met moeite en blijf in bed

### Onderdeel 3: Tillen
- Ik kan een zwaar voorwerp zonder extra pijn tillen
- Ik kan een zwaar voorwerp tillen maar dat doet extra pijn
- Ik kan door de pijn geen zware voorwerpen van de grond optillen, maar het lukt me wel als ze op een handige plaats staan, bijv. op tafel
- Ik kan door de pijn geen zware voorwerpen tillen maar wel lichte tot middelzware als ze op een handige plaats staan
- Ik kan alleen lichte voorwerpen tillen
- Ik kan niets tillen of dragen

### Onderdeel 4: Stappen
- Pijn voorkomt niet dat ik ver kan stappen
- Pijn voorkomt dat ik verder kan stappen dan 2 km
- Pijn voorkomt dat ik verder kan stappen dan 1 km
- Pijn voorkomt dat ik verder kan stappen dan 100 m
- Ik kan alleen met een stok of krukken lopen
- Ik breng het grootste deel van de tijd in bed door

### Onderdeel 5: Zitten
- Ik kan in elke stoel zitten zolang als ik wil
- Ik kan alleen in mijn favoriete stoel zitten zolang als ik wil
- Ik kan door de pijn niet langer dan een uur blijven zitten
- Ik kan door de pijn niet langer dan een half uur blijven zitten
- Ik kan door de pijn niet langer dan 10 minuten blijven zitten
- Ik kan door de pijn helemaal niet zitten

### Onderdeel 6: Staan
- Ik kan staan zolang ik wil zonder extra pijn te krijgen
- Ik kan staan zolang ik wil maar dat veroorzaakt extra pijn
- Door de pijn kan ik niet langer dan 1 uur blijven staan
- Door de pijn kan ik niet langer dan 30 minuten blijven staan
- Door de pijn kan ik niet langer dan 10 minuten blijven staan
- Door de pijn kan ik niet blijven staan

### Onderdeel 7: Slapen
- Mijn slaap wordt nooit door pijn onderbroken
- Mijn slaap wordt af en toe door pijn onderbroken
- Door de pijn slaap ik minder dan 6 uur
- Door de pijn slaap ik minder dan 4 uur
- Door de pijn slaap ik minder dan 2 uur
- Door de pijn slaap ik in het geheel niet

### Onderdeel 8: Het seksleven (indien toepasbaar)
- Mijn seksleven is normaal en beoordeel ik geen extra pijn
- Mijn seksleven is normaal maar beoordeel ik wel extra pijn
- Mijn seksleven is bijna normaal maar erg pijnlijk
- Mijn seksleven wordt ernstig beperkt door de pijn
- Mijn seksleven is vrijwel afwezig door de pijn
- Door de pijn heb ik in het geheel geen seksleven meer

### Onderdeel 9: Het sociale leven
- Mijn sociale leven is normaal en beoordeel ik geen extra pijn
- Mijn sociale leven is normaal maar beoordeel ik wel extra pijn
- Met uitzondering van de meer inspannende bezigheden zoals sport heeft de pijn geen belangrijke invloed op mijn sociale leven
- De pijn heeft mijn sociale leven beperkt en ik ga minder vaak de deur uit
- Door de pijn is mijn sociale leven beperkt tot mijn eigen huis
- Ik heb geen sociaal leven vanwege de pijn

### Onderdeel 10: Reizen/Transport
- Ik kan overal naar toe reizen zonder extra pijn
- Ik kan overal naar toe reizen maar heb dan extra pijn
- De pijn is weliswaar erg maar ik kan toch reizen maken die langer duren dan 2 uur
- Door de pijn kan ik niet langer reizen dan 1 uur
- Door de pijn kan ik slechts korte, noodzakelijke tochtjes maken die korter duren dan 30 minuten
- Door de pijn ga ik alleen maar de deur uit om naar de dokter of het ziekenhuis te gaan
S2 5: Dutch version of SF-12-questionnaire for Discogel® injection.

Deze vragenlijst gaat over uw kijk op uw gezondheid. Met behulp van deze gegevens kan worden bijgehouden hoe u zich voelt en hoe goed u in staat bent uw dagelijkse bezigheden uit te voeren. Dank u voor het invullen van deze vragenlijst!

Beantwoord elk van de volgende vragen door een X in het hokje te plaatsen dat het meest overeenkomt met uw antwoord.

1. Hoe zou u over het algemeen uw gezondheid noemen?
   - Uitstekend
   - Zeer goed
   - Goed
   - Matig
   - Slecht

2. De volgende vragen hebben betrekking op bezigheden die u misschien doet op een doorsnee dag. Wordt u op dit moment bij deze bezigheden beperkt door uw gezondheid? Zo ja, in welke mate?
   - Ja, ernstig beperkt
   - Ja, een beetje beperkt
   - Nee, helemaal niet beperkt
   a. Matige inspanning, zoals een tafel verplaatsen, stofzuigen, zwemmen of fietsen
   b. Een paar verdiepingen opgaan

3. Hoe vaak heeft u tijdens de afgelopen 4 weken ten gevolge van uw lichamelijke gezondheid de volgende problemen bij uw werk of andere dagelijkse bezigheden gehad?
   a. U heeft minder bereikt dan u zou willen
   b. U was beperkt in het soort werk of andere bezigheden

4. Hoe vaak heeft u ten gevolge van emotionele problemen (zoals depressieve of angstige gevoelens) tijdens de afgelopen 4 weken de volgende problemen ondervonden bij uw werk of andere dagelijkse bezigheden?
   a. U heeft minder bereikt dan u zou willen
   b. U deed uw werk of andere bezigheden niet zo zorgvuldig als gewoonlijk

5. In welke mate bent u de afgelopen 4 weken door pijn gehinderd in uw normale werk (zowel werk buitenshuis als huishoudelijk werk)?
   - Helemaal niet
   - Een klein beetje
   - Nogal
   - Veel
   - Heel erg veel
6. Deze vragen gaan over hoe u zich voelt en hoe het met u ging de afgelopen 4 weken. Zou u bij elke vraag dat antwoord geven dat het best benadert hoe u zich voelde. Hoe vaak gedurende de afgelopen 4 weken –

<table>
<thead>
<tr>
<th></th>
<th>Altijd</th>
<th>Meestal</th>
<th>Soms</th>
<th>Zelden</th>
<th>Nooit</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Voelde u zich rustig en ontspannen?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>b. Had u veel energie?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>c. Voelde u zich somber en neerslachtig?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

7. Hoe vaak hebben uw lichamelijke gezondheid of emotionele problemen u gedurende de afgelopen 4 weken gehinderd bij uw sociale activiteiten (zoals vrienden of familie bezoeken, enz.)?

<table>
<thead>
<tr>
<th></th>
<th>Altijd</th>
<th>Meestal</th>
<th>Soms</th>
<th>Zelden</th>
<th>Nooit</th>
</tr>
</thead>
</table>

*Dank u wel voor het beantwoorden van deze vragen!*
3. Scientific output

S3 1: Case report Tijdschrift voor Geneeskunde, ‘Beeld van de Maand’ (under review).

MRI van de Sacro-iliacale gewrichten volgens ASAS criteria: rol in diagnose van actieve Spondylarthritis

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2 Universiteit Hasselt, Diepenbeek
3 ReumaClinic, Genk

Ziektegeschiedenis

Een 43 jarige man klaagt reeds 1 jaar van continue lage rugpijn, bilateraal uitstralend naar de dijachtervlakte en liezen. De pijn begon geleidelijk, verbeterde met beweging, maar echter niet bij rust. De pijn was ook ‘s nachts aanwezig, voornamelijk in de tweede helft van de nacht, waardoor de patiënt wakker werd, en ging gepaard met ochtendstijfheid van een uur. Verdere systeem- en familiale anamnese was negatief. Klinisch onderzoek toonde een mobiliteitsbeperking van de dorsale en lumbale wervelkolom, drukpijn gluteaal bilateraal, en een positief teken van Patrick. Lasègue-manoeuvre was negatief evenals screening neurologisch onderzoek van de onderste ledematen. Uit bloedonderzoek bleek dat de patiënt HLA-B27 positief was; CRP was normaal. Standaard radiografisch onderzoek van het bekken wees op een mogelijke sacroiliitis graad 1 rechts en graad 2 links, waarbij de modified New-York criteria voor ankylooserende pelvispondylitis niet gehaald werden. Op basis van een CT-scan werd spondylartropathie (SpA) vermoed met sacroiliitis en erosies van de sacroiliacale gewrichten (SIG). Er werd gestart met NSAIDs (piroxicam 20mg/dag, later overgeschakeld op naproxen 1000mg/dag) en oefentherapie, waardoor de klinische toestand van de patiënt beterde, maar niet voldoende. De nachtelijke rugpijn persisteerde met irradiatie naar de lies en de gluteale regio. Klinisch behield de patiënt een pijnlijke bewegingsbeperking op lumbaal en cervicaal niveau. Ondertussen liep de BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) op tot 6,1/10. Behandeling met anti-TNF werd overwogen, mede gezien onvoldoende respons op voorafgaand gebruik van minimum 2 NSAIDs (piroxicam en naproxen) gedurende 3 maanden. Terugbetalingscriteria voor anti-TNF werden evenwel niet gehaald gezien het normaal CRP. Er werd dan een MRI van de SIG uitgevoerd waarbij multipale zones van subchondraal boteodeem beiderzijds vastgesteld werden, wijzend op actieve osteitis letseels (positief MRI onderzoek volgens de Assessment of SpondyloArthritis international Society (ASAS) criteria). Met behulp van dit MRI onderzoek werd besloten dat de SpA bij deze patiënt zich in een actief inflammatoire fase bevond, ondanks de normale CRP-waarde. Uiteindelijk kon de patiënt op deze basis geïncludeerd worden in een wetenschappelijk studie met biologicals, waarmee hij opvallend verbeterde.
Bespreking

MRI heeft de sensitiviteit voor de diagnose van SpA aanzienlijk verhoogd wegen de visualisatie van zowel de vroege, acuut inflammatoire veranderingen als de chronische structurele letsels van SpA. MRI is de beeldvormingstechniek bij uitstek om SpA in het vroege, non-radiografische stadium te detecteren. Een CT-scan daarentegen toont enkel chronische, structurele veranderingen aan bot en/of gewrichten (figuur 1), en zal de diagnose van SpA in het inflammatoire stadium niet kunnen stellen (1). Een vroege en correcte diagnose is belangrijk om een behandeling tijdig te initiëren, om te voorkomen dat de acute letsels evolueren naar structurele veranderingen. Een tweede voordeel van MRI tegenover CT is dat de patiënt niet blootgesteld wordt aan ioniserende straling.

Een grote vooruitgang in het gebruik van MRI voor de diagnose van SpA was de ontwikkeling van de ASAS criteria in 2009 (2). De ASAS criteria zijn opgebouwd uit een beeldvormingszijde en een klinische zijde, waarbij de patiënt aan één van de twee zijdes moet voldoen om de diagnose SpA te krijgen. De klinische zijde vereist HLA-B27 positiviteit en minstens 2 andere SpA kenmerken. Voor de beeldvormingszijde moet sacroiliitis aangetoond worden op beeldvorming (radiografie of MRI) en moet de patiënt minstens 1 SpA kenmerk vertonen. MRI beelden worden best uitgevoerd in para-axiale en paracoronale richting, waarbij T1-gewogen beelden vooral nuttig zijn om chronische, structurele veranderingen op te sporen en waarbij T2-gewogen beelden met vetsaturatie en ‘short tau inversion recovery’ (STIR) beelden gevoelig zijn voor de detectie van subchondraal botoedeem (osteitis, acute beenmerginflammatie) (figuur 1) (3). Sacroiliitis op MRI van de SIG wordt gedefinieerd als duidelijke aanwezigheid van één letsel met acute beenmerginflammatie op minstens 2 opeenvolgende sneden, ofwel minstens 2 letsels op dezelfde snede. Voor spondylitis op MRI van de wervelkolom geldt dat er minstens 3 letsels zichtbaar moeten zijn, telkens op minstens 2 sneden.
Voor patiënten met ≥ 3 maanden rugpijn waarbij de klachten begonnen op een leeftijd < 45 jaar

**Beeldvormingszijde**

- Sacroiliitis op beeldvorming
  - EN ≥ 1 SpA kenmerk*

**Klinische zijde**

- HLA-B27 positief
  - EN ≥ 2 andere SpA kenmerken*

*Sacroiliitis op beeldvorming:

- acute inflammatie op MRI
  - hoog suggestief voor sacroiliitis geassocieerd met SpA, of
- duidelijke radiografische sacroiliitis volgens de gemodificeerde New York criteria

*SpA kenmerken:

- inflammatoire rugpijn
- artritis
- enthesitis
- uveitis
- dactylitis
- psoriasis
- ziekte van Crohn/colitis ulcerosa
- goede initiële respons op NSAIDs
- familiale geschiedenis van SpA
- HLA-B27 aanwezigheid
- verhoogde CRP waarde

De radiografie van de SIG van deze patiënt vertoonde geen bilaterale sacroiliitis van minstens graad 2 noch een unilaterale sacroiliitis van minstens graad 3, de CT toonde sacroiliitis met erosies, maar het MRI onderzoek was doorslaggevend voor de diagnose van de aanwezigheid van actieve inflammatie via visualisatie van het subchondrale botoedeem, waarbij de ASAS criteria voor SpA gehaald werden. De betere diagnostiek die met behulp van MRI verkregen wordt, helpt de behandelende geneesheer om de meest efficiënte behandeling voor de patiënt te kiezen. Dit onderschrijft de rol van MRI van de SIG voor patiënten met non-radiografische SpA met betrekking tot betere en vroegtijdige diagnose.
Figuur 1:
A: CT-scan van de SIG in het para-axiale vlak toont de chronische, structurele veranderingen, zoals erosies met omgevende beenderige sclerose (zwarte pijlen). Acute, inflammatoire letsels zijn niet zichtbaar.
B: Op dit STIR MRI beeld van de SIG in het paracoronale vlak zijn zowel acute als chronische veranderingen zichtbaar. Noteer vooral de bandvormige hyperintense letsels in het subchondrale bot van beide SIG (witte pijlen), wijzend op inflammatie/oedeem van het subchondrale beenmerg. Conform met de ASAS criteria is dit MRI onderzoek positief voor acute, inflammatoire SpA.

Conclusie
MRI is de beeldvormingstechniek bij uitstek voor de diagnose van SpA omdat het zowel acute inflammatoire fasen als chronische letsels in beeld brengt. CT en radiografie kunnen ook suggestief zijn voor de diagnose van SpA, maar zullen enkel structurele, chronische botletsels detecteren. Door gebruik te maken van MRI kan de diagnose van SpA in een vroeger stadium gesteld worden (actieve, niet-radiografische stadium) of kan heropflakkering van inflammatorisch stadium van SpA worden aangetoond: dit verbetert de diagnose en helpt de behandelende geneesheer bij het kiezen van geschikte medicatie voor de patiënt om de ontwikkeling van chronische veranderingen te verhinderen.

Abstract
A 43 year old male presented with symptoms of inflammatory low back pain. Plain film and CT showed structural bone changes (erosions) within the sacro-iliac joints, and inflammatory spondylarthropathy (SpA) was suggested. MRI was key to demonstrate the active phase of SpA based on visualization of subchondral bone edema (osteitis) on top of the chronic, structural bone changes; subsequently, effective treatment was initiated.

MRI is the imaging modality of choice to demonstrate both acute inflammatory lesions and chronic structural lesions within the sacro-iliac joints. The MRI examinations are analyzed by the radiologist according to the ASAS criteria for SpA (Assessment of SpondyloArthritis international Society). MRI of the sacro-iliac joints may be instrumental to select the most effective therapy by demonstrating the active phase of SpA.
Referenties


Cone Beam CT to Assess Bony Fusion Following Anterior Cervical Interbody Fusion

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ABSTRACT

Purpose: Assessment of bony fusion following anterior cervical interbody fusion (ACIF) is usually done by plain film or CT. We present the first clinical application of Cone-Beam CT (CBCT) to evaluate bony fusion after ACIF.

Methods: A 56-year-old man with disc herniation at C6-C7 underwent ACIF surgery using a compressed nanocrystalline hydroxyapatite interbody device (nanOss-C, Pioneer Surgical Marquette, MI) and a nanocrystalline hydroxyapatite bone graft filler (nanOss Bioactive, Pioneer Surgical Marquette, MI). Imaging follow-up was performed by CBCT (NewTom 5G, QR Srl., Verona, Italy) at one day, 6 weeks, 3 months and 9 months postoperatively. Two independent assessors quantitatively measured the greyscale changes of the bone graft filler and qualitatively evaluated the bony fusion process.

Results: Quantitative analysis of the images showed a steadily increasing matrix density of the bone graft filler over the 9 months follow-up, suggesting increasing calcification. Qualitative evaluation demonstrated different stages of the bone fusion process within the disc space around the cage, at the interface between cage and endplates, and at the interface between bone graft filler and the endplates.

Conclusions: CBCT provides high-resolution cross-sectional imaging of the cervical spine after ACIF. For the first time, in vivo evaluation of the bone graft filler within the center of the circumferentially radiodense cage and detailed cross-sectional evaluation of bone fusion was achieved. Confirmation of these promising outlooks of CBCT in a large cohort of ACIF patients is needed with regard to routine clinical application and evaluation of different interbody devices.

KEYWORDS

Cone-beam CT, ACIF procedure, fusion, greyscale
INTRODUCTION

Cone Beam CT (CBCT) is an advancement in CT imaging that provides a potentially low-dose cross-sectional technique for visualizing bony structures. To date, this has primarily been used in dental and maxillofacial imaging. [1] CBCT was first developed as a tool for clinical use in 1982 at the Mayo Clinic Biodynamics Research Laboratory. [2] In the intervening years, several CBCT systems have been developed for use both in the interventional suite as well as the originally intended general applications such as CT angiography. [3, 4]

As CBCT imaging systems have become more widely available, there has been an increasing interest in the intraoperative and diagnostic use of CBCT for applications in the extra-cranial head and neck regions. It is likely that the strongest aspects of CBCT, i.e. the high isotropic spatial resolution reaching 100 μm or less, the relative low radiation dose requirements and fewer metal artifacts are characteristics that have made it particularly attractive as a valuable diagnostic technique. [5-7] In the head and neck region, where the vascular and bony structural anatomy is particularly complex, the ability to discriminate fine anatomic detail can provide a much more effective clinical tool. [8]

However, despite the advantages over other imaging modalities, there has been little use of CBCT in cervical vertebrae imaging. Furthermore, while it has been used to assess bone structure in maxillofacial and dental surgery, both pre- and post-operatively, it has not been used as a tool to assess bony fusion following cervical interbody fusion. We are therefore reporting on the first use of CBCT to evaluate osseous changes following anterior cervical interbody fusion (ACIF).
METHODS/CASE REPORT

**Patient:** The patient was a 56 year old male who presented in our clinic with symptoms of radicular tingling in his right arm and paresthesia in his index and middle finger of his right hand. Clinical evaluation and MRI was performed to identify the involved cervical level. He was diagnosed with disc herniation on the right side at C6-C7. Initial treatment consisted of a series of 3 cervical epidural infiltrations at level C6-C7 resulting in 90% improvement. However, troublesome paresthesia continued and he was subsequently scheduled for ACIF surgery.

**Treatment:** An anterior cervical interbody fusion was performed using a 7 mm compressed nanocrystalline hydroxyapatite interbody device (nanOss-C, Pioneer Surgical Marquette, MI) with a nanocrystalline hydroxyapatite bone graft filler (nanOss Bioactive, Pioneer Surgical Marquette, MI). The vertebrae were fixed with a titanium anterior plate using self-drilling screws. The hospitalization occurred without complications, radicular pain disappeared and the patient was discharged 1 day post-operatively.

**Cone Beam CT:** The CBCT used in this report was a NewTom 5G CBCT (QR Srl, Verona, Italy). The patient was positioned with the cage in the middle of the CT bore by adjusting the height of the table and with the cage as parallel as possible with the middle of conic X-ray beam. The cone beam volume scan was acquired with a 12x8 field of view and a spatial resolution of 150 µm, and reconstructed to axial images with isotropic voxel resolution of 0.5 mm. Images were reformatted in the sagittal and coronal plane with a width of 1 mm at 1 mm intervals. The mean radiation dose the patient experienced for each CBCT scan was 7.94 mGy (computed tomography dose index or CTDI). The patient was assessed one day after surgery and then at 6 weeks, 3 months, and 9 months.

**Data Analysis:** The CBCT images were assessed quantitatively to investigate the density changes of the bone graft filler and qualitatively to evaluate signs of bony fusion. Qualitative evaluation of bony fusion included descriptive observations regarding bony changes at the interface between cage and bone, between bone graft filler and bone, and within the disc space.

Quantitative evaluation of CBCT images was done by measuring the greyscale units, as the X-ray attenuation in CBCT is displayed by grey levels. Although, these grey values do not allow for direct bone quality assessment, a recent study reported a linear relationship between CT Hounsfield Units (HU) and greyscale when using the NewTom 5G CBCT. [9] This is the same device currently used in our hospital, which is the reason we used grey value measurements as an assessment of bone density. All images were evaluated by 2 independent assessors at each time point. The greyscale values were measured using a region-of-interest (ROI) measuring tool and recorded. In order to normalize the greyscale data, the screws and the cage were used as reference values, as the density of these materials will not change over time. Therefore, the ratio of the greyscale value of the bone graft inside the cage and the greyscale value of the cage or screw were calculated as a means of measuring the change in the radiodensity of the hydroxyapatite bone void filler.
RESULTS

1. Quantitative

There was a very high agreement between the 2 assessors with regard to the measured greyscale values. The Pearson correlation coefficients for the scores from the 2 independent evaluators ranged from 0.987 to 0.998 with an absolute difference ranging from a low of 0.02% to a maximum of 9.8%.

Over the 9 months of post-operative measurement, there was a steady increase in the measured values, as shown in Figure 1. Figure 1 depicts the change in the radio-opacity for the bone void filler over the 9 months of follow-up. Specifically, this represents the greyscale values of the graft material normalized to the greyscale values of the interbody cage. Similar changes were seen when the data were also normalized to the greyscale level of the screws used to fix the anterior plate.

Fig. 19 The increasing greyscale value of the bone void filler over the post-operative follow-up. The points on the chart depict the ratio in greyscale intensity between the hydroxyapatite bone void fill and that of the intervertebral cage.
2. Qualitative

With regard to qualitative assessment of the images, views in the sagittal and axial planes are presented in Figures 2 and 3.

Regarding bone formation within the disc space posteriorly to the cage, firstly radiodense thickening of the endplates is seen in the form of stalactites and stalagmites (at 1 month), followed by gradually filling in of the disc space with hazy densities representing matrix mineralization (progressively at 3 and 6 months). Finally at 9 months, CBCT images show an almost solid trabecular bone bridge. Whilst at a single sagittal image, this bone bridge extending from the vertebra below to the vertebra above may seem a thin pillar, the axial CBCT images demonstrate that the bony fusion consists of left-to-right broad struts.

Another qualitative finding consists of the bone changes at the interface between the cages and the endplates. Already at 1 month, dense sclerotic bone change is seen underlying the endplates at the pressure areas with the cage wall. These pressure areas in this case are at the posterior half of the cage. On the sagittal image, the sclerotic bone change has the shape of the hood of a mushroom on top of its stalk (the cage wall). This sclerotic bone change becomes only slightly wider in shape at the different time points. Subsidence of the cage into the vertebral body is not seen.

A third qualitative finding relates to the changes at the interface between the bone graft filler and the endplates. One day after surgery a clear radiolucent line is seen in between, which gradually changes into a radiodense area representing bony integration of the bone graft filler with the vertebral body. Bony integration is first seen with the vertebra above (at 1 month) and later with the vertebra below (at 9 months). Note that metal artifacts were present as broad, slightly radiodense bands running obliquely through the image on both sides of the anterior plating.

Axial CBCT images demonstrate the ability of CBCT to evaluate the radiodensity of the bone graft filler within the circumferentially radiodense cage, not possible on radiographs. The density of the bone graft filler inside the cage gradually increases over the different time points. (Figure 3) We also observed the appearance of hazy densities posteriorly of the cage 1 month after the surgery, which increased in amount and density 3 months post-operatively, and have changed into trabecular bone at 9 months post-operatively.
Fig. 20 Sagittal CBCT images of 1 day, 1 month, 3 months and 9 months post-operatively provide qualitative assessment of bony changes at the interface between cage wall and vertebral endplates, in the intervertebral disc space, and between bone graft filler and vertebral endplates. Dense sclerotic bone apposition underlying the endplates is seen at the interface between the posterior cage wall and vertebral endplates, resembling the hood of a mushroom on its stalk (cage wall): reactive bone changes at pressure points (black arrows).

In the disc space posteriorly, bony apposition to the endplates in the form of stalactites and stalagmites are seen together with hazy densities in the center (matrix mineralization), resulting in solid trabecular bone fusion at 9 months (white arrows). The radiolucent line between bone graft filler and the endplates fills in with radiodense material (above at 1 month and below at 9 months), representing osseointegration of the bone graft filler with the endplates.

Fig. 21 Axial views at 1 day, 1 month, 3 months and 9 months post-operatively enables assessment of bone graft filler density and qualitative bone formation in the disc space around the cage. CBCT allows the measurement of radiodensity changes of the bone graft filler within a circumferentially radiodense cage, not possible with radiography or classic CT scan. Note that the density of the bone graft filler inside the cage gradually increases over the different time points.

The CBCT images at 1 month and 3 months show hazy densities in the disc space posteriorly to the cage, representing bone mineralization, followed by a solid trabecular bone bridge at 9 months (white arrows). Another strut of bone fusion can be seen developing on the left anterolateral side of the disc space (arrow (black arrow)). CBCT allows for appreciation of the width and size of the bone formation within the disc space around (posteriorly and laterally of) the cage. Note the width of the hazy densities (bone mineralization) posteriorly to the cage, a width that can not be seen with either radiography or classic CT scan.
DISCUSSION

CBCT provides high-resolution cross-sectional imaging of the cervical vertebrae in the presence of metal implants while maintaining a low radiation dose. In this case report, CBCT was successfully used to evaluate the process of bony fusion after ACIF. For the first time, in vivo imaging evaluation of the bone graft filler within the center of a circumferentially radiodense hydroxyapatite cage was achieved, both quantitatively and qualitatively. Quantitative density measurements using greyscale units showed a steady increase in bone graft filler density over the course of 9 months. Greyscale analysis of CBCT images had a very high agreement between the independent investigators. Qualitatively, bony integration of the bone graft filler with the adjacent vertebrae was shown as disappearance of the radiolucent line in between. Both these findings have yet not been possible neither with radiographic or classical CT imaging.

Of note, while the greyscale values of the images provided by CBCT do not allow the direct determination of HU, the accepted standard for measuring radiodensity and thus matrix calcification in the process of bone formation, recent work by Razi, et al. (2014) has demonstrated a linear relationship between CBCT greyscale and HU. Their work was done using the same type of CBCT that we used (NewTom 5G CBCT) and thus supports the feasibility of our method in assessing density changes.

The high resolution cross-sectional technique of CBCT offers the advantage of a detailed qualitative evaluation of the bone fusion process. Besides the subchondral sclerotic bone changes at the pressure areas of the cage wall with the endplates, different stages of the bone fusion process were shown in the periphery of the cage: bone apposition adjacent to the endplates, appearance of hazy densities indicating matrix calcification/mineralization, and finally formation of trabecular bone within the disc space. Appreciation of the amount and width of these changes was possible with this cross-sectional technique, not demonstrated before with radiography nor with classical CT. With regard to ACIF outcomes, with the use of CBCT the amount of bone mineralization is visible, as there are the hazy densities visible before a stable bone bridge is formed. [9, 10, 11]

In comparison to conventional CT imaging, CBCT delivers a lower radiation dose to the patient. In a comparison between effective radiation dose of CBCT and Multislice CT (MSCT) scanners for dental and maxillofacial applications, effective dose values ranged from 13 to 82 μSv for CBCT and from 474 to 1160 μSv for MSCT. [5] Similar data concerning a significant decrease in radiation dose values have been reported elsewhere. [4, 6] Considering the number of scans or radiographic examinations obtained in a typical ACIF procedure, from initial diagnosis through the end of treatment, it seems prudent then to limit the patient’s exposure and therefore obviate the potentially deleterious effects of radiation exposure. In our own measurements, one CBCT examination exposed the patient to only one fourth of the radiation dose compared to a classic CT scan.

Another advantage of CBCT is that metal artefacts do not influence CBCT image quality as much as they do with classical CT. [12, 13] Most ACIF procedures will use some manner of metal implant, either stainless steel or titanium, in the procedure. Admittedly, CBCT does suffer from artefact immediately next to the anterior plate. [14, 15] This does not, however, extend to the entire volume involved in the fusion procedure, and the artefact diminishes rapidly with distance from the implant. [15] Therefore, while a small percentage of the imaged volume will be affected by implant artefact, CBCT still provides good imaging
quality through the overwhelming majority of the imaged volume. In our case, metal artefacts of the anterior plate were seen as slightly radiodense bands running obliquely through the image. These artifacts did not prohibit the qualitative evaluation of bony changes at the ACIF level. Quantitative information was expected to be influenced by these metal artefacts, but we tried to minimize this influence by positioning the patient identically at each time point resulting in a comparable metal artefact for each scan.

As an imaging technique, CBCT offers some clear advantages over CT or radiographs. As with any tool and original applications, it is necessary to develop the full potential in this specific function. Further research is warranted to determine the best way to analyze CBCT images. It would be helpful to expand on the initial work by Razi, et al. (2014) and further elucidate the relationship between HU and CBCT greyscale measure, as well as the relationships between the greyscale units and fusion, bony ingrowth and trabecular bridging. [9] Further studies should examine the variability of changes as observed in imaging during the process of bone fusion using a large patient cohort. While our study presents the first use of CBCT to assess bone fusion following ACIF, this pilot work supports the clinical application to analyze bone fusion process in detail and also supports the potential to study in vivo the osseointegration of the bone graft filler within the cage.

Acknowledgments
We acknowledge Paul Trégouët for his assistance with medical writing.

Conflict of interest
Jan Vandevenne and Leen Wijnen have no financial interest in RTI Surgical. Dieter Peuskens is a clinical investigator for RTI Surgical. The authors have no conflict of interest in this study.
The Postfusion Spine: “to fuse or not to fuse”

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Fusion surgery is often performed in patients with low back pain or neck pain when conservative therapy has failed: the degenerated disc is removed and replaced by a fusion implant or cage composed of bone graft (auto-graft), allograft or an artificial substitute. The surgical level is often stabilized with an anterior plate, rods and/or screws. Besides preserving the height of the disc space, another function of the cage is to stimulate bone healing in the intervertebral space. When bony fusion between the two adjacent vertebrae is achieved, these two vertebrae behave as one solid piece of bone.

Examples of fusion surgeries include anterior cervical interbody fusion (ACIF), anterior lumbar interbody fusion (ALIF), posterior lumbar interbody fusion (PLIF), transforaminal lumbar interbody fusion (TLIF) and extreme lateral interbody fusion (XLIF).

At postoperative follow-up, the surgeon wants to know whether there is

- (ongoing) fusion or pseudarthrosis
- correct position and integrity of the instrumentation
- any complication

The radiologist needs to monitor the process of bony fusion by interpreting the sequential changes visible on plain film. Plain films (anteroposterior, lateral views in flexion and extension) are the mainstay of radiological evaluation. In order to evaluate signs of (ongoing) fusion on plain films, the radiologist can use the Food and Drug Administration (FDA) fusion criteria. These criteria include evidence of trabecular bone bridging between the 2 involved vertebrae (between vertebral endplates, facets, pedicle or transverse processes), an angular motion of less than 5° and a translational motion of less than 3 mm (measured on flexion and extension images).

Features which can be analyzed in order to assess signs of ongoing fusion are the gradual disappearance of a radiolucent line around the cage, the gradual appearance of hazy matrix calcification followed by trabecular bone formation in the intervertebral space (often first on the posterior side of the cage), and the rotational and translational immobility on flexion/extension views. Ongoing pseudarthrosis may be suspected when a radiolucent line around the cage persists or broadens, when interbody bone formation is sharply delineated with sclerotic borders instead of continuously bridging, when the instrumentation appears loose or fractured or when a change in subsidence and position of the cage is seen at flexion/extension views.

The radiologist may use plain film or CT to evaluate correct position of screws, rods, anterior plating and interbody devices (non radio-opaque devices usually contain markers). Disadvantages of CT over plain films are the higher radiation exposure and the presence of beam hardening artefacts caused
by the instrumentation. MRI is superior to detect myelum or nerve root compression (if not hindered by metal artefacts), including adjacent level degeneration; SPECT-CT is superior to evaluate for loosening of screws and for visualization of pseudarthrosis (highest accuracy if more than one year postoperative).
Discogel® Injection for Painful Monosegmental Black Disc

Introduction

Painful monosegmental black disc is a particular cause of chronic low back pain in young active adults. Compared to surgical treatments, Discogel® injection is a minimally invasive treatment equally aiming to reduce the discogenic pain. The aims of this proof of concept study were to evaluate the clinical outcome and to estimate the economic effect.

Material and Methods

Six patients (4 men, 2 women, mean age 35yrs) with painful monosegmental black disc, unresponsive to conservative therapy, were included. Treatment consisted of fluoroscopy-guided intradiscal injection of 0,4-0,8ml Discogel®. The Visual-Analogue-Scale (VAS) and Oswestry-Disability-Index (ODI) were scored pre-operatively, 1-day, 3-weeks and 6-weeks post-operatively. Change in work status or sport activity was noted. Patient invoices were analyzed comparing the cost of Discogel® injection and fusion surgery.

Results

One day post-injection, the mean VAS-score was 17% worse than pre-operatively. At 6 weeks, 4 patients had a good result (improvement of VAS-score >70% or 2 points, improvement of ODI-score >50%), 1 patient had a moderate result (VAS-score unchanged, ODI-score 13% improved) and 1 patient had a poor result (scores unimproved). Five out of six patients were back to work or normal sport activity within 6 months. Discogel® treatment has a 80,4% lower cost than fusion surgery.

Conclusion

Discogel® injection looks promising to treat young active patients with painful monosegmental black disc. Treatment with Discogel® may avoid fusion surgery, is cheaper than surgery, and is associated with high return to work. Confirmation in a larger patient cohort is necessary.
Discogel® Injection for Painful Monosegmental Black Disc

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INTRODUCTION

Chronic low back pain is an important health problem in young active adults. A common cause of chronic low back pain is painful monosegmental black disc. When conventional medical and rehabilitation therapy fail, fusion surgery is often considered in order to treat the discogenic pain. Discogel® injection is devised as a minimally invasive treatment to reduce discogenic pain. The active component is ethyl alcohol: it is postulated to cause dehydration of the nucleus pulposus and to have a destructive effect on the nerve endings in the annulus fibrosus tear.

AIM

The aims of this proof of concept study were:
1. to evaluate the clinical outcome of patients who received a Discogel® injection
2. to estimate the economic effect of this minimally invasive treatment option.

MATERIALS & METHODS

Study design

6 young, active patients (4 men, 2 women, avg. age 35 years) with painful monosegmental black disc included for fusion surgery were included.

Discography + Discogel® injection

Follow-up time points: 1 day, 3 weeks and 6 weeks post-procedure

Outcome measures:

1. Clinical outcome
   - VAS-score: pain intensity
   - ODI-score: functional disability

2. Estimated economic effect
   - compare patient invoices of fusion surgery versus Discogel® injection
   - hospital stay, pharmaceutical costs, device costs and surgical fees
   - change in work or sport status

RESULTS & DISCUSSION

1. Clinical outcome

   Initial increase in pain intensity and functional disability (1 day after the procedure), followed by a strong decrease 3-6 weeks after the procedure (see tables and graphs).

2. Estimated economic effect

   - Discogel® injection had a 80.4% lower cost than fusion surgery. The lower costs were attributed to a shorter hospital stay (day clinic), lower pharmaceutical costs and lower surgeon fees.
   - 8 out of 6 patients were back to work or normal sport activity within 6 months.

REFERENCE

Discogel® injection looks a promising minimally invasive treatment for young active patients with painful monosegmental black disc. Treatment with Discogel® may avoid fusion surgery, is cheaper than surgery, and is associated with high return to work. Confirmation of these results is necessary in a larger patient cohort with a longer follow-up.

CONCLUSION

Abbreviations

VAS: Visual Analogic Scale
ODI: Oswestry Disability Index

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*Advanced radiological techniques regarding spinal fusion*

Richting: **master in de biomedische wetenschappen-klinische moleculaire wetenschappen**
Jaar: **2015**

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