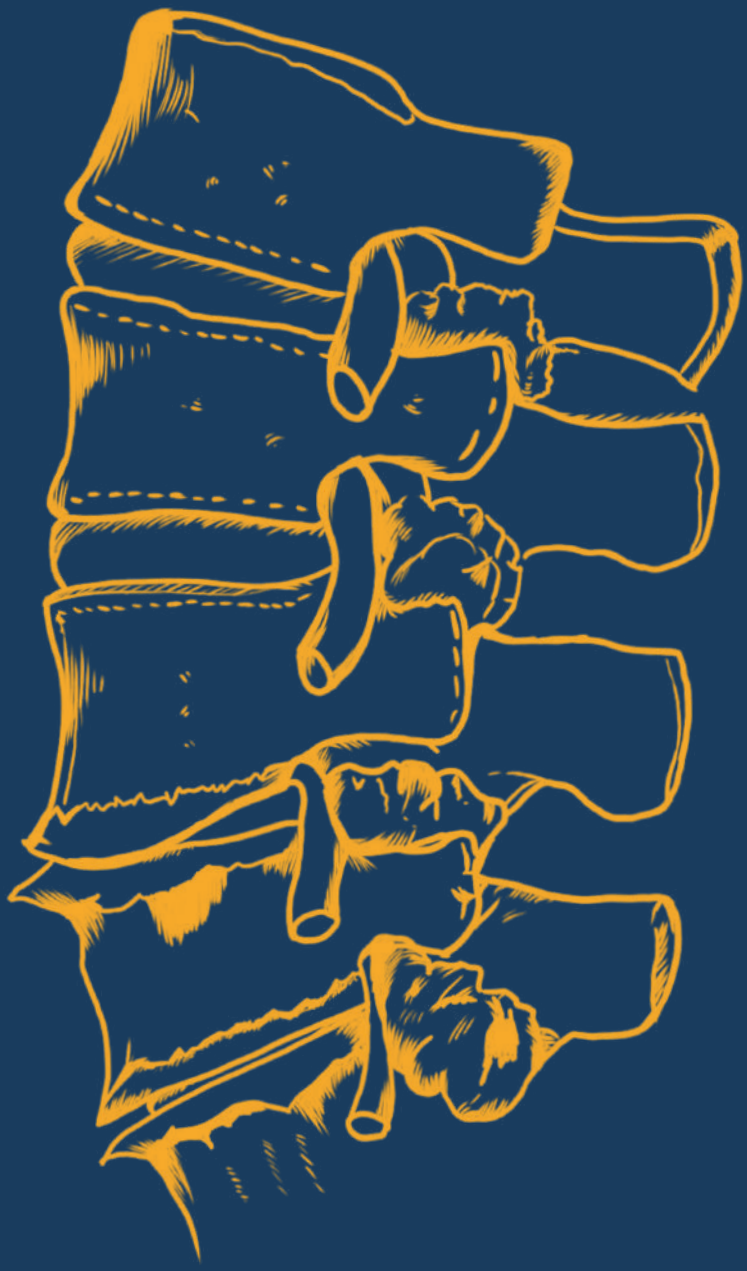
CHALLENGES IN THE TREATMENT OF DEGENERATIVE INTERVERTEBRAL DISC DISORDERS

FROM FUSION TO TRACTION



ROEL KERSTEN

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FROM FUSION TO TRACTION

ROELAND FREDERIK MARK RAYMOND KERSTEN

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Challenges in the treatment of degenerative intervertebral disc disorders

From fusion to traction

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Van fusie tot tractie
(met een samenvatting in het Nederlands)

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The SNAP trial: a double blind multi-center randomized controlled trial of a silicon nitride versus a PEEK cage in transforaminal lumbar interbody fusion in patients with symptomatic degenerative lumbar disc disorders: study protocol. **Kersten RFMR**, van Gaalen SM, Arts MP, Roes KC, de Gast A, Corbin TP, Öner FC. *BMC Musculoskeletal Disord, 2014 Feb;15:57*

Polyetheretherketone (PEEK) cages in cervical applications: a systematic review. **Kersten RFMR**, van Gaalen SM, de Gast A, Öner FC. *Spine J 2015 Jun 1;15(6):1446-60*

Lumbar spinal fusion: indications, surgical technique and postoperative management. A survey among spine surgeons in the Netherlands. **Kersten RFMR**, van Gaalen SM, Willems PC, Arts MP, Peul WC, Öner FC. *MOJ Orthop Rheumatol 2016;4(5):00155*

Temporary segmental distraction in a dog with degenerative lumbosacral stenosis. Willems N, **Kersten RFMR**, van Gaalen SM, Öner FC, Strijkers GJ, Veraa S, Beukers M, Tryfonidou MA, Meij BP. *Vet Comp Orthop Traumatol 2018 Jul;31(4):298-303*

Comparison of polyetheretherketone versus silicon nitride intervertebral spinal spacers in a caprine model. **Kersten RFMR**, Wu G, Pouran B, van der Veen AJ, Weinans HH, de Gast A, Öner FC, van Gaalen SM. *J Biomed Mater Res B Appl Biomater 2019 Apr;107(3):688-699*

Surgical restoration of sagittal alignment of the spine: correlation with improved patient-reported outcomes: a systematic review and meta-analysis. Ochtman AEA, Kruyt MC, Jacobs WCH, **Kersten RFMR**, le Huec JC, Öner FC, van Gaalen SM. *JBJS Rev 2020 Aug;8(8)e1900100*

Are the Roland Morris Disability Questionnaire and the Oswestry Disability Index interchangeable in patients with degenerative lumbar disc disorders? **Kersten RFMR**, Fikkers J, Wolterbeek N, Öner FC, van Gaalen SM. *J Back Musculoskeletal Rehabil 2021;34(4):605-611*

The SNAP trial: two-year results of a double blind multi-center randomized controlled trial of a silicon nitride versus a PEEK cage after lumbar fusion surgery. **Kersten RFMR**, Öner FC, Arts MP, Mitroiu M, Roes KCB, de Gast A, van Gaalen SM. *Global Spine J 2021 Jan;7:219256822098472*

Letter to the editor regarding "Two-year results of a double-blind multicenter randomized controlled non-inferiority trial of polyetheretherketone (PEEK) versus silicon nitride spinal fusion cages in patients with symptomatic degenerative lumbar disc disorders". **Kersten RFMR**, Öner FC, Arts MP, Mitroiu M, Roes KCB, de Gast A, van Gaalen SM. *Global Spine J 2021 Jun;7(2):249-251*

Table of Contents

1

GENERAL INTRODUCTION AND THESIS OUTLINE

Introduction

Low back pain (LBP) is a major health problem throughout the world with an estimated point prevalence of 10.2% and a life-time prevalence of up to 84% (1-4). It represents the number one cause for outpatient clinic visits worldwide (5). Approximately one in five patients report persistent back pain 1 year after their first episode, resulting in consistent limitations in daily life (2). It is the most common cause of activity limitation and work absence throughout the world, resulting in high socio-economic costs and loss of quality of life (6-8). In the US, it is estimated that management of chronic LBP cost nearly $85 billion annually (9, 10). Worldwide it is the leading cause of years lost to disability, with 83 million disability-adjusted life years lost in 2010 (11-13). It is expected that the total number of chronic LBP patients will increase due to population growth and aging (8).

Degenerative disc disorders (DDD) are associated with chronic LBP, with multiple population-based studies reporting strong correlations between LBP and DDD (14-18). The underlying cause of DDD, also referred to as natural aging of the spine, is considered to be multifactorial; genetic inheritance, aging, trauma, infections, obesity, diabetes, smoking and loading history play a role (19-25). It includes a vicious circle of a catabolic cell response, changed extracellular matrix and altered biomechanics of the intervertebral disc (IVD) (26). Mechanical loading is identified as the most important extrinsic contributor to degeneration of the IVD. The reason remains subject to debate, as mechanical loading is also a major preservator of disc homeostasis (19, 27, 28).

Anatomy

The IVD is the central part of the spinal motion segment and lies between the vertebral bodies. Its main function is to absorb axial compressive forces on the spine and to facilitate load transmission, allowing flexion, extension, bending and rotation (5, 29). The IVD is the largest avascular structure of the body and composed of three anatomical structures: the gelatinous nucleus pulposus (NP) at its center, surrounded by the annulus fibrosis (AF) and the cartilaginous and bony endplates that anchors onto the vertebrae (26, 30-32). The NP is a highly hydrated tissue, rich in proteoglycans and collagen type II fibers, generating osmotic pressure and resisting

axial loads (5, 26, 30). The AF is a fibrocartilaginous structure that provides tensile strength to the IVD by containing and maintaining the osmotic pressure of the NP. The outer layer of the AF consists of 20-25 concentric lamellae, composed mainly of parallel bundles of collagen type 1 orientated at oblique angles providing tensile strength. The inner part of the AF serves as a transition zone and has a higher type II collagen and proteoglycan content compared to the outer zone, providing resistance to compressive loading (5, 19, 32). The cartilage and bony endplates surround the IVD cranial and caudal, and are thought to be responsible for most of the nutrients exchange.

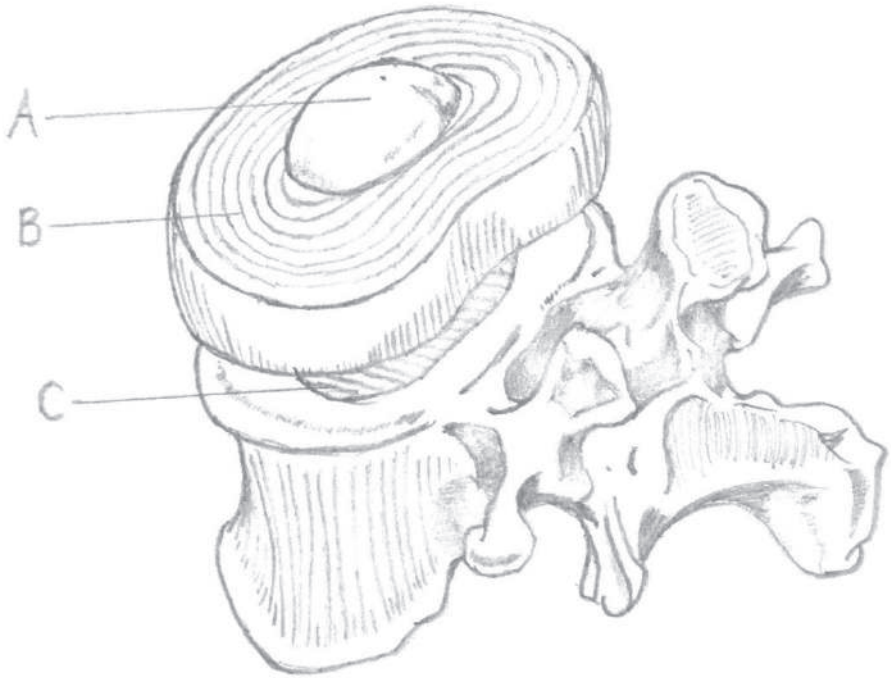

Figure 1. *The intervertebral disc consists of the inner nucleus pulposus (A) , surrounded by the annulus fibrosis (B) and lies between the vertebral endplates (C).*

Pathogenesis of DDD

Degeneration of the IVD usually starts in the NP. A decrease in proteoglycans causes the NP to lose its capability to retain and absorb water, resulting in loss of disc height. Subsequently, due to a loss of intradiscal pressure from the NP, the AF deforms causing structural defects like rim lesions and radial fissures possibly leading

to disc herniation's and obstruction of neural structures in the vertebral canal (19, 26, 27). Also, microscopic and macroscopic changes to the endplate can lead to impairment of nutrition of the IVD and endplate sclerosis (33, 34). These endplate lesions include proliferating nerves, which are susceptible to chemical and mechanical stimulation, causing low back pain (35, 36). Degenerated IVDs have been shown to be innervated with nociceptive nerves, providing support for the existence of discogenic pain (19, 37). Disc degeneration can initiate secondary changes leading to facet joint osteoarthritis, spondylolisthesis and spinal stenosis causing radiculopathy and neurogenic claudication with or without LBP (13, 14). Abnormal movement in the affected motion segment can cause pain (14, 38, 39). Also, lumbar disc herniation coincides with degeneration of the IVD (40, 41).

Treatment options for DDD

Because there is no curative therapy for DDD, treatment strategies are directed at symptom relief. Various conservative interventions for DDD exist, including physical- and manual therapy, cognitive behavioral treatment, interdisciplinary rehabilitation, multidisciplinary pain management programs, pharmacological treatment (acetaminophen, non-steroidal anti-inflammatory drugs (NSAID's), opioids, antidepressants) and invasive pain treatments such as nerve blocks for patients with accompanying radiculopathies due to nerve root compression (42-44).

If patients do not respond to conservative care, surgical interventions may be indicated. The lumbar total disc replacement (TDR) aims to relieve pain by replacing a degenerated IVD with a mobile prosthesis, thereby aiming to restore the functional anatomy and biomechanics (45). Significant improvement in clinical outcome is reported in literature after TDR in patients DDD, but concerns remain on the high revision rates of 6-14% due to malposition, subsidence and loosening (19, 42, 46). Also, there are a lot of contraindications for TDR, including spondylolisthesis, scoliosis, facet joint osteoarthritis and spinal stenosis (45-47). The current best available evidence suggests that TDR may be an effective treatment for a select group of patients with DDD, comparable with spinal fusions the first few years. However, considering the long-term disadvantages, spine surgeons should be cautious about performing TDR on a large scale (48). As a result, only a small percentage of patients currently diagnosed with surgery for DDD are indicated for TDR, ranging from 5 – 14% (46, 49).

Spinal fusion (with decompression in case of nerve root- or spinal cord compression) of a symptomatic spinal motion segment is the most commonly used surgical treatment option for patients with DDD suffering both from significant back- and leg pain. It is designed to eliminate movement of the degenerated spinal motion segment by achieving an arthrodesis. Good results have been reported in literature for reducing pain and improving function (42, 50, 51). The number of patients undergoing fusion surgery and subsequent costs of these procedures have increased significantly, especially in the US (52, 53). For example, the annual number of spinal fusion surgeries in the US increased 2.4 fold from 174.223 to 413.171 between 1998 and 2008. The total costs for spinal fusion increased 7.9 fold to $33.9 billion in 2008. This was significantly greater than the increases in hip replacement and knee arthroplasty (3.5 fold and 5.1 fold respectively (52). This can be partially explained by the aging of the population, but also financial aspects may play a role.

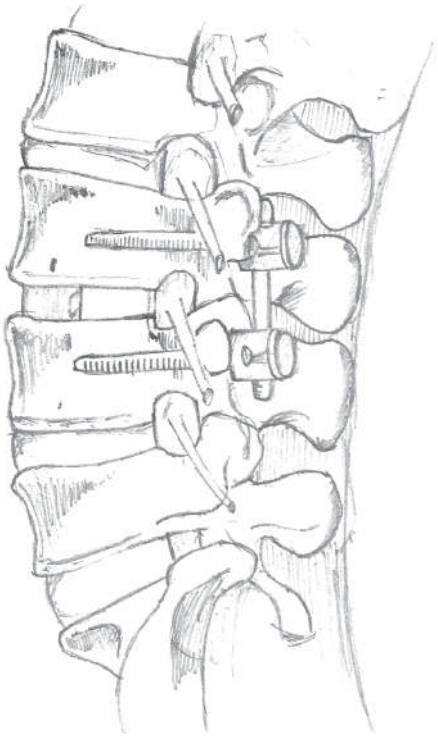

Figure 2: *Spinal fusion with pedicle screws & rods. The degenerated intervertebral disc is replaced by an interbody cage, to achieve a bony fusion between the two vertebrae.*

Mechanical and biologic factors in addition to the implant material being used all play an important role in creating an optimal environment for bony fusion correcting spinal degenerative deformities (54-56). Therefore, different types of implant geometry, combined with different implant materials and/or surface coatings, have been investigated to improve fusion rates and functional outcomes of spinal fusions (57-63, 63). Several surgical techniques like the posterolateral fusion (PLF), posterior lumbar interbody fusion (PLIF), transforaminal lumbar interbody fusion (TLIF) and anterior lumbar interbody fusion (ALIF) have been developed (51, 53, 64-67). In the last decade, this armamentarium has ever been enriched with oblique lumbar interbody approaches (OLIF), anterior to psoas and lateral techniques (XLIF) (68, 69). Still, consensus regarding spinal fusion is lacking among spinal surgeons on indications, surgical techniques, implant materials and postoperative care (42, 65, 70, 71). The global community would benefit from uniform and consistent counseling, for which consensus is essential. If we want to continue to improve the outcome for spinal fusion surgery, it is important to understand how we came to the current mode of practice (72).

The history of spinal fusion

The foundation for spinal fusion surgery was laid in the 19th century (72, 73). Traumatic injuries, Pott`s disease (spinal tuberculosis) and congenital disorders were the first spinal cases treated with a surgical spinal fusion procedure (72, 74). The Hadra wiring technique was introduced in 1891 as the first surgical instrumentation to enhance fusion, in which adjacent spinous processes were bound together using a metal wire in a figure of 8 in a patient with an 8-month old fracture dislocation (75). Autologous bone grafts, taken from the spinous processes, were already being used in the early 20th century to promote spinal fusion, as described separately by Albee and Hibbs in 1911 in patients with Pott`s disease (76, 77). By the 1930s, the first spinal fusions to treat degenerative disc disorders were performed, using autograft taken from the iliac crest in combination with Hadra wiring. Also, the first anterior fusion was described in a 14-year old boy treated for traumatic spondylolisthesis of L5-S1. (73). Interbody fusion was introduced in 1944 by Briggs and Milligan. They described a posterior approach to access the intervertebral space and replace it with an autologous bone peg to augment an interbody fusion, a precursor to modern day PLIF (72). Facet screws were added in the late 1940s by King, hereby immediately obtaining rigid

fixation, avoiding prolonged brace immobilization (78). With the Harrington rod, originally developed in 1962 for correction of severe post-polio scoliosis, internal fixation techniques accelerated and the rod was quickly used for other conditions including spondylolisthesis and trauma (79, 80). The first allografts were introduced in spinal surgery in 1976. They provided an osteoconductive environment allowing bone ingrowth in an anterior cervical fusion model (81). But high failure rates due to collapse, subsidence and resorption of the bone grafts were frequently seen in lumbar fusion surgery (82, 83). Therefore, during the 1980s, interbody cages were developed as an alternative for bone grafts. The cages were designed to contain bone graft allowing bony fusion of the affected segments. Also, they restore and maintain disc- and foraminal height. The Bagby and Kuslich (BAK) cage, originally developed for cervical spine stabilization in horses, was adapted in 1988 for human lumbar fusion and showed fusion rates up to 88% (84, 85). Various interbody cages made of Titanium (Ti) were commercialized in the subsequent years (50, 86, 87). However, a disadvantage of solid Ti cages was their interference with radiographic imaging, which makes visualization of bone formation especially on computed tomography (CT) scans and spinal cord/soft tissue visualization on magnetic resonance imaging (MRI) more difficult. Polyetheretherketone (PEEK) cages were developed as an alternative during the late 1990s. They were radiolucent and produced fewer artefacts on MRI and CT compared to Ti. Moreover, their Young`s modulus, close to that of cancellous bone, presumably reduced the stress shielding (54, 88). PEEK cages have since been widely used during the past 20 years and still hold a dominant position in the spinal implant markets being most surgeon's preferred implant material of choice for spinal fusion (88-90). However, PEEK as a synthetic plastic has a hydrophobic surface, discouraging osteointegration. This is believed to increase the risk for subsidence and migration of the cage (91-94). Therefore, the latest developments focus on PEEK with Ti-coatings and hydroxyl-apatite (HA) coatings to improve direct bone-implant contact ratios (95, 96). Other developments include trabecular metal (tantalum), carbon-fiber reinforced PEEK and bio-absorbable cages (97-100). Also, ceramic materials entered the market, such as silicon nitride (Si_3N_4). Si_3N_4 is a non-oxide ceramic that is partially radiolucent and reduces artefacts on CT and MRI imaging (60, 101, 102). Several *in vitro and in vivo* studies have confirmed the biocompatibility and osteoconductive qualities of Si_3N_4 (103-106). Also, decreased bacterial activity has been reported on the surface of Si_3N_4 compared to PEEK and Ti (93, 107). Si_3N_4 received the CE Mark and FDA

clearance in 2008 for its use as an interbody cage in spinal fusion, and was expected to decrease complications such as non-union and subsidence. However, clinical data with long-term follow-up are paramount but not yet available.

Developments during the last decades

As non-union remains a challenge in spinal fusion surgery, researchers started to investigate the potential of alternative graft materials with appropriate osteoconductive and/or osteoinductive properties. Examples were bone morphogenetic protein-2 (BMP-2) and osteogenic protein-1 (OP-1 / BMP-7). They were shown to initiate and enhance new bone formation, but later also became associated with complications like ectopic bone formation, even possibly with increasing cancer risks (108, 109). In the last decade we have seen a transition from mesenchymal stem cell therapy and tissue engineering to cage surface modulations in order to stimulate protein binding and improve osteointegration (110-112).

Also, researchers have been investigating strategies that restore the functional integrity of the intervertebral disc by temporary distraction of the intervertebral disc (113) . This technique was derived from temporary joint distraction of the osteoarthritic ankle and knee joint, allowing for regeneration of cartilage (114, 115). Because of similarities between articular cartilage and the IVD, distraction is suggested to initiate a biological repair process of the degenerated IVD. Also, it may even prevent future adjacent segment changes that would otherwise be triggered by a formal fusion, as the pedicle screw construct in the case of a distraction does not remain *in situ* for a long period of time (116, 117). *In vivo* rabbit models showed signs of tissue repair at a biological, cellular and biomechanical level after distraction of the degenerated IVD (113). The safety and clinical efficiency of temporary distraction of the IVD needs to be investigated in future studies. Lastly, over the last decades analysis of sagittal alignment of the spine has been emphasized. Many spine surgeons are convinced that restoration of spinopelvic parameters would lead to better clinical improvement in spinal fusion cases (118-121). However, currently there is still only limited evidence that surgical restoration of the spinal sagittal alignment may significantly improve patient reported outcome (122).

Defining treatment outcome

For comparing the effectiveness of different treatments for patients presenting with symptomatic DDD, assessment of radiographic and clinical outcome following treatment is essential (123). The ability to identify a successful fusion is considered an important element in the management of patients undergoing lumbar interbody fusion procedures (124). But fusion seems to be a poorly defined definition, resulting in a lack of consensus how to radiographically determine a successful fusion. Also, scientific evidence on the correlation between a successful fusion and good clinical outcome is still scarce. Besides fusion, patient-reported outcome measures (PROMS) represent an important method to assess the quality of care from the patient's perspective, and are widely accepted and recommended in clinical guidelines (123, 125-127). During the last decades, a large variety of validated PROMS have been widely used for the assessment of outcome of treatment in patients with LBP. For example; the Short Form 36- Health Survey (SF-36) to measure the generic health status, the Visual Analog Score (VAS) for pain intensity and the Oswestry Disability Index (ODI) and the Roland Morris Disability Questionnaire (RMDQ) to evaluate the functional status of patients ((128-131). However, there is no consensus in the spinal community which questionnaire should be used and how the results should be interpreted, which makes comparison between different treatment options difficult. Also, there is ongoing debate on the amount of improvement that classifies for a clinical success (132-134). Therefore, there is also a need for clear recommendations on determining outcome.

AIM AND OUTLINE OF THE THESIS

This thesis is structured by subdividing the research in several parts:

Part I. Current practice
Part II. Challenges in surgical fusion techniques: SNAP trial
Part III. Challenges in therapeutic strategies and outcome measurement

The following research questions were formulated for this thesis.

Part I. Current practice

1. *What is the current practice regarding lumbar spinal fusion among spinal surgeons in the Netherlands?*

Spinal fusion is commonly used for treatment of degenerative disc disorders. However, there is no consensus among spinal surgeons on indications, operative technique, the type of implant being used and postoperative care. In **Chapter 2**, the results of an online 30-question survey, sent to all members of the Dutch Spine Society (DSS), are presented.

2. *What is the evidence for the use of PEEK cages as preferred implant material for spinal fusion in patients with degenerative disc disorders?*

PEEK cages have been widely used during the past decades and hold a dominant position as the preferred implant material for spinal fusion. Their radiolucency and low Young's elastic modulus make them attractive for spinal fusion in patients with degenerative disc disorders. Still, drawbacks are seen, such as non-union and migration of the cage (90, 135, 136). In **Chapter 3** the clinical and radiological outcome of PEEK cages compared with other interbody cages was evaluated with a systematic review of the literature. Because only a limited number of lumbar interbody fusion studies were found in the literature, with large variations in operative techniques and indications for surgery, only cervical interbody fusion studies were included.

Part II. Challenges in surgical fusion techniques: SNAP trial

3. *Are ceramic silicon nitride cages an alternative for PEEK cages to improve the outcomes for spinal fusion in patients with degenerative disc disorders?*

PEEK is bio inert and does not effectively osteointegrate due to a fibrous tissue surrounding PEEK (91, 92, 94). Hence, other implant materials are being investigated. Ceramic implants made of Si_3N_4 show better biocompatibility and osteoconductive quality and are therefore expected to lower complication rates and allow for better

fusion (93, 106, 107). In **Chapter 4** the fusion rates, bony apposition and bone volume formation between PEEK and silicon nitride cages are evaluated in an *in vivo* observational study. A caprine model is used because of similarities in the axial loads, disc geometry and morphology between the intervertebral discs of humans and goats (137). To compare the clinical outcome and fusion rates of PEEK cages with Si_3N_4 cages in patients with symptomatic lumbar degenerative disc disorders, the 'Silicon Nitride And PEEK' (SNAP) trial was designed. In **Chapter 5** the study protocol of this non-inferiority multicenter randomized controlled trial (RCT) is presented. The protocol is published to improve transparency and provides a full overview of the methods in this study**. Chapter 6** comprises the 2-year follow-up results of this RCT.

Part III.Challenges in therapeutic strategies and outcome measurement

4. *Is temporary disc distraction a viable treatment option for degenerative disc disorders?*

Temporary distraction of the joint reduces the mechanical stress, prevents further wear and allows for repair of the cartilage in patients with osteoarthritis of the ankle and knee (111, 112). Because of the similarities between articular cartilage and the intervertebral disc, segmental distraction of the intervertebral disc could allow biological repair of the affected disc and might prevent adjacent segment degeneration (113). In **Chapter 7**, a pilot study is presented to investigate the safety and efficiency of temporary distraction of an intervertebral disc with signs of degeneration in a dog. Distraction was applied for 3 months with a follow-up of 6 months.

5. *What is the role of sagittal alignment in the treatment of patients with degenerative disc disorders?*

Analysis of the sagittal alignment of the spine has become more important in the treatment of patients with DDD. But there is little direct evidence that surgical restoration of the spinal sagittal alignment improves patient related outcome. (100) (100)(97)(94) The aim of **Chapter 8** is to assess the correlation between actually

obtained spinal sagittal alignment and PROMS in patients that were surgically treated for lumbar DDD. A meta-analysis of the available literature was conducted.

6. *Are the Roland Morris Disability Questionnaire (RMDQ) and the Oswestry Disability Index (ODI) interchangeable in patients with degenerative disc disorders after spinal fusion?*

For optimizing clinical decision making and evaluation of treatment it is important to evaluate the functional status of patients with PROMS. The RMDQ and ODI are frequently used. But comparison of results of these two questionnaires is difficult due to differences in content, structural validity and scoring systems. **Chapter 9** determines if the RMDQ and ODI are exchangeable to improve comparison of treatment results.

Finally, a summary and general discussion of the main findings of this thesis are provided in **Chapter 10**. It evaluates the current literature, discusses the main limitations and focuses on the opportunities for further research.

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PART I.

CURRENT PRACTICE

2

LUMBAR SPINAL FUSION: INDICATIONS, SURGICAL TECHNIQUE AND POSTOPERATIVE MANAGEMENT. A SURVEY AMONG SPINE SURGEONS IN THE NETHERLANDS

MOJ ORTHOP RHEUMATOL 2016;4(5):00155

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ABSTRACT

Study design: Cross sectional study

Objective: Spinal fusion is commonly used for treatment of degenerative disc disorders. However, there is no consensus among spinal surgeons on operative technique, the type of implant being used and postoperative care. With the growing importance of Evidence Based Medicine, the demand for clinical guidelines is increasing. The aim of this study was to provide an overview of the current practice regarding lumbar spinal fusion among spinal surgeons in the Netherlands. The findings of this enquiry may help to create guidelines.

Methods: an online 30-question survey was sent to all members of the DSS (orthopedic surgeons and neurosurgeons), focusing on operative techniques, implants and post-operative care after spinal fusion in patients with symptomatic degenerative conditions of the lumbar spine.

Results: the response rate was 66%. The bilateral PLIF technique with 2 cages was preferred by most surgeons. Neurosurgeons used a PEEK cage more often, whereas orthopedic surgeons preferred a titanium cage. There was no consensus on assessment of outcome of fusion and post-operative care.

Conclusions: There is little consensus among spine surgeons in the Netherlands regarding perioperative management, type of instrumentation and implants, operation technique, and postoperative management in lumbar spinal fusion in patients with symptomatic degenerative disc disorders, which underlines a growing demand for uniform guidelines.

INTRODUCTION

Low back pain (LBP) is a major health problem with a life-time prevalence up to 84% (1). Degenerative disc disorders (DDD) are held responsible (2). Several surgical and non-surgical treatment options have been developed to reduce pain and improve function, including spinal fusion (3). However, large variation in clinical outcome has been reported (4, 5). This difference can be partially explained by the lack of consensus for indications for surgery (5). Moreover, there are several surgical techniques and implant materials for performing spinal fusion (4, 6). Also, post-operative rehabilitation may play an important role in the outcome of surgery, with multidisciplinary cognitive-behavioral interventions as one of the latest developments (7). Finally, there is no global consensus which clinical and radiographic outcome measures should be used to determine the outcome of surgery (4).

With the growing importance of Evidence Based Medicine, the demand for clinical guidelines is increasing. Patients, care givers, insurance companies and policymakers have a need for uniform and consistent counseling, for which consensus in clinical practice is essential. In 2014 the Nijmegen decision tool was published (8). A Delphi approach was used to determine 47 indicators, which help referring a patient with chronic low back pain (CLBP) to the proper caregiver (surgical or non-surgical). It is the first step in reducing costs and improving the outcome of spinal interventions.

Purpose

The aim of this study was to provide an overview of the current surgical practice for degenerative lumbar conditions among spinal surgeons in the Netherlands. Subsequently, the findings of this enquiry will be compared to the updated guidelines for the performance of fusion procedures for degenerative disease of the lumbar spine, published in 2014 by the North American Spine Society (NASS) (9).

MATERIALS AND METHODS

Design

Cross-sectional study

Patient sample and data management

On February 1, 2013, an online 30-question survey was sent by e-mail to all members (orthopedic surgeons and neurosurgeons) of the Dutch Spine Society (DSS). It contained a web link to the online survey, a brief introduction, background rationale and 3-week timeline for completion of the questionnaire. Also, the confidential and voluntary nature was addressed. Return of the questionnaire was considered as consent to participate. Joomla (Open Source Matters Inc) was used to administer the survey and collect the data.

A reminder email was sent after one month. Final call for participation was made on the annual congress of the DSS on November 8, 2013.

Outcome measures

The questionnaire consisted of 30 multiple choice questions focusing on operative techniques, implant materials and post-operative care after spinal fusion in patients with symptomatic degenerative conditions of the lumbar spine (L1-S1). Also, the criteria for symptomatic disc degeneration (SDD) were addressed, since these play an important role in the indication for surgery. Additionally, the outcome of surgery was assessed. The questionnaire was evaluated and revised by two orthopedic surgeons, two neurosurgeons and a clinical researcher prior to distribution. Participants were asked to rely on their own experience regarding the indications, technique, materials and post-operative care for elective spinal fusion operations.

Data analysis

Data were downloaded and entered into Microsoft Excel (Microsoft Corp., Redmond, Washington, USA). All personally identifiable data were deleted. Unanswered questions were coded as missing. Statistical analyses were performed with Statistical Package for the Social Sciences software (SPSS 22.0, SPSS Inc., Chicago, Illinois, USA). Descriptive statistics were used to describe the main characteristics. Pearson's X^2 test was used to evaluate if the answers were significantly different. Significance level was set at $p<0.05$. If the conditions for the Chi-square test were not matched the Fischer's exact test was used.

RESULTS

Participants

The survey was sent to all 158 members of the DSS, comprising 101 orthopedic surgeons and 57 neurosurgeons. 79 of the surveyed surgeons had either ended their surgical practice or did not perform lumbar spinal fusion for degenerative conditions. Of the remaining 79 surgeons, 52 (66%) responded. The characteristics of the final group are listed in table 1. A majority of the respondents (65%) preferred open surgical approach. The self-reported average duration of surgery was less than 150 minutes in 83% of the respondents. There was no significant difference in the level of clinical experience between the orthopedic surgeons and neurosurgeons (p=0.67). The self-reported average duration of surgery did not differ between orthopedic surgeons and neurosurgeons (p=0.82).

Table 1. Characteristics

	"Orthopedic surgeons (n)"	"Neuro-surgeons (n)"	"Discipline not specified (N)"	All (n)
No. of respondents				
	32 (62%)	18 (34%)	2 (4%)	52 (100%)
No. of fusions/year				
< 25	17 (53%)	7 (39%)		24 (46%)
> 25	15 (47%)	11 (61%)	2	28 (54%)
Years of experience				
< 10	14 (44%)	7 (39%)		21 (40%)
> 10	17 (53%)	11 (61%)	1	29 (56%)
Unknown	1 (3%)		1	2 (4%)
Preferred technique				
Open	22 (69%)	12 (67%)		34 (65%)
Minimal invasive	10 (31%)	6 (33%)	2	18 (35%)
Average operation time				
< 90 min	4 (13%)	2 (11%)		6 (12%)
90-150 min	23 (72%)	12 (67%)	2	37 (71%)
> 150 min	4 (12%)	4 (22%)		8 (15%)
Unknown	1 (3%)			1 (2%)

Disc degeneration on imaging

Table 2 lists the aspects related to symptomatic disc degeneration (SDD). Pfirrmann et al described a T2-weighted MRI grading system for lumbar disc degeneration, which is often used in clinical practice (10). A majority of respondents (52%) did not use the Pfirrmann scale on MRI (10) as a measure for SDD, but 54% related Modic changes on MRI to SDD. The majority of the respondents (75%) did not relate the vacuum phenomenon on CT or plain radiographs to SDD, and 58% did not use provocative discography to diagnose SDD. 67% of the respondents who performed < 25 fusions a year considered loss of disc height as a sign of SDD whereas only 39% of the respondents with >25 fusions a year did (p=0.05). There was no relation with clinical experience (p=0.60). There was a significant difference amongst orthopedic surgeons and neurosurgeons interpreting loss of disc height on plain radiographs as a sign of SDD, 69% vs 28% respectively (p=0.01). Also, orthopedic surgeons used the Pfirrmann score significantly more often compared to neurosurgeons, 59% vs 33% respectively (p=0.05).

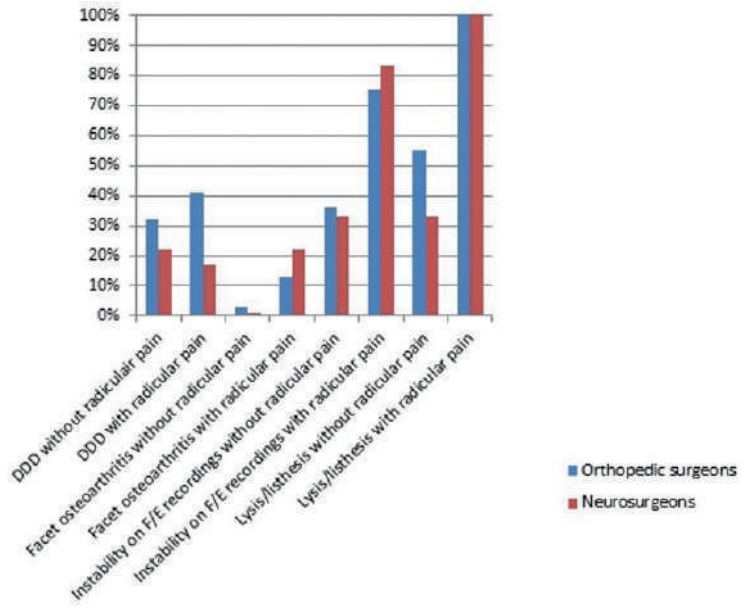
Table 2. Relating symptomatic disc degeneration to one of the following aspects

	"Orthopedic surgeons (n)"	"Neurosurgeons (n)"	"Discipline unknown (n)"	"All (n)"	p-value
Loss of disc height on a X-ray					**0.01**
Yes	22 (69%)	5 (28%)	-	27 (52%)	
No	10 (31%)	13 (72%)	2	25 (48%)	
Disc degeneration on MRI (Pfirrmann scale)					**0.05**
≥ Grade 1	1 (3%)	-	-	1 (2%)	
≥ Grade 2	-	-	-	-	
≥ Grade 3	13 (41%)	3 (17%)	-	16 (31%)	
≥ Grade 4 or 5	5 (16%)	3 (17%)	-	8 (15%)	
No	13 (41%)	12 (67%)	2	27 (52%)	
Modic changes on T1 MRI					**0.96**
Yes	18 (56%)	10 (56%)	-	28 (54%)	
No	14 (44%)	8 (44%)	2	24 (46%)	
Vacuum phenomenon on CT/X-ray					**0.26**
Yes	10 (31%)	3 (17%)	-	13 (25%)	
No	22 (69%)	15 (83%)	2	39 (75%)	
Recognizable pain upon provocative discography					**0.36**
Yes	15 (47%)	6 (33%)	1	22 (42%)	
No	17 (53%)	12 (67%)	1	30 (58%)	

Indication for surgery

Indications for spinal fusion surgery are listed in figure 1. A minority of respondents (28%) would perform a spinal fusion on patients who presented with DDD causing LBP without radicular pain. A majority of these surgeons (71%) related loss of disc height on plain radiograph to SDD. Moreover, the majority of these surgeons related a Pfirrmann score ≥grade 3 (64%) and Modic changes on MRI (86%) to SDD. A minority of these surgeons also related a vacuum phenomenon (29%) to SDD. Provocative discography was related to SDD by half of these surgeons (50%). Overall, there were no significant differences between orthopedic surgeons and neurosurgeons in indications for surgery. Spondylolisthesis with radicular pain was considered an indication for surgery by all respondents.

Figure 1. Indications for spinal fusion



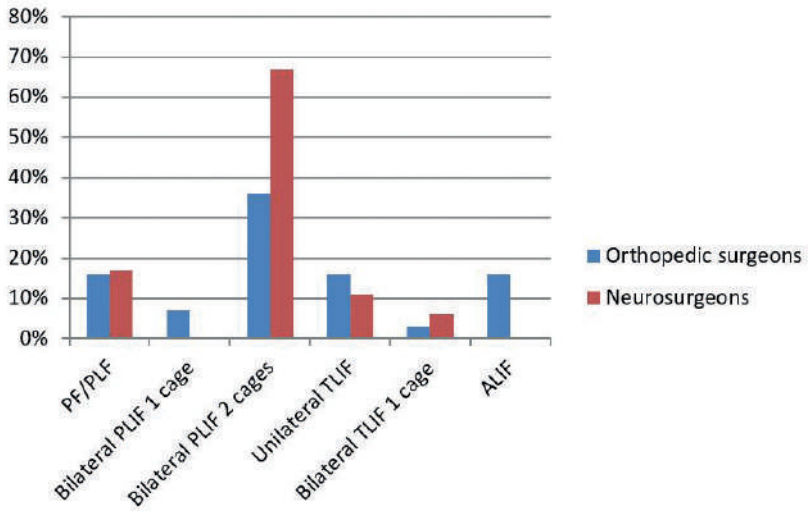
Abbreviations used: DDD = degenerative disc disease, F/E = flexion/extension

Operation techniques

The most commonly used fusion techniques are listed in Figure 2. All respondents used pedicle screw fixation during a lumbar spinal fusion. The bilateral posterior lumbar interbody fusion (PLIF) with 2 interbody cages was the most used additional

surgical technique (44%). A majority of respondents did not change their surgical technique in case of spondylolisthesis (73%), symptomatic central stenosis (77%) or foraminal stenosis (79%). Neurosurgeons used the technique with a bilateral PLIF with 2 interbody cages significantly more often than orthopedic surgeons, 67% vs 36% respectively (p=0.04). There was no relation with years of experience and fusion technique (p=0.86). Neurosurgeons reported to remove significantly more of the disc than orthopedic surgeons; 25% of the orthopedic surgeons reported to remove less than 50% of the disc, whereas all neurosurgeons reported to remove more than 50% (p=0.04). Of all the respondents, 67% reported to remove more than half of the disc.

Figure 2. Standard fusion techniques

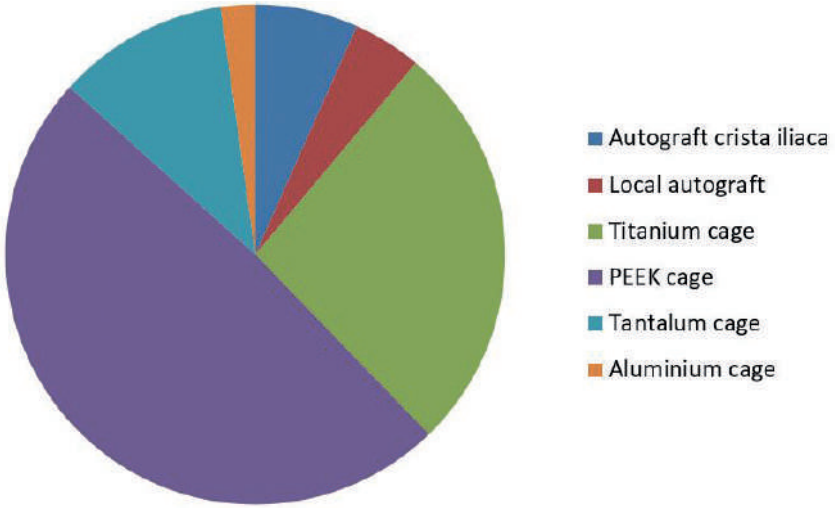


Abbreviations used: PF/PLF = posterior/posteolateral fusion, PLIF = posterior lumbar interbody fusion, TLIF = transforamina lumbar interbody fusion, ALIF = anterior lumbar interbody fusion

Interbody implants and types of grafts:

The implants used for interbody fusion are listed in figure 3. The most commonly used material was a polyetheretherketone (PEEK) cage (44%). The majority of the respondents (56%) considered local autologous bone graft (harvested from the lamina) to be the best option for cage filling. Neurosurgeons used a PEEK cage significantly more often than orthopedic surgeons did, 78% vs 25%, respectively (p<0.01). Orthopedic surgeons preferred a titanium cage significantly more often compared to neurosurgeons, 34% vs 6%, respectively (p=0.02).

Figure 3. Standard materials used for interbody fusion



Abbreviations used: PEEK = polyetheretherketone

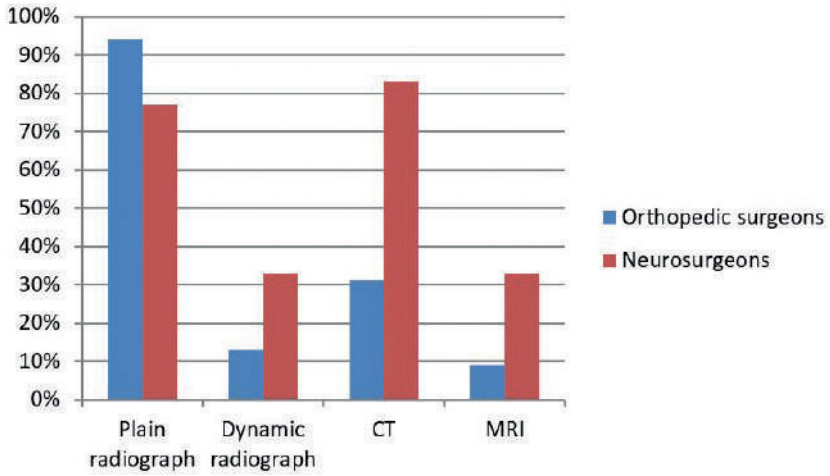
Post-operative care:

For postoperative pain treatment 79% of the respondent's prescribed intravenous patient controlled analgesia (PCA) with morphine, 6% PCA-spinal/epidural morphine, 46% non-steroidal anti-inflammatory drugs (NSAIDs), 48% acetaminophen/perfalgan, 15% opioids and 10% used local anesthesia. None of the respondents used gabapentin or pregabalin. Perioperative antibiotics were used for 24 hours by 60% of the respondents, 39% prescribed a single dose of prophylactic antibiotics. 37% of spinal surgeons prescribed anticoagulants (low molecular weight heparin (LMWH)) postoperatively, mainly for 4-6 weeks. A vast majority of the respondents (94%) allowed patients to mobilize within 24hrs after surgery. 64% of spinal surgeons recommended against the use of a lumbar orthosis postoperatively, although all of the surgeons (100%) who reported to prefer a posterior/posterolateral fusion (PF/PLF) procedure recommended the use of a lumbar orthosis postoperatively. Within this group there were no significant differences between orthopedic surgeons and neurosurgeons (p=0.48) or years of experience (p=0.88) Referral to a physical therapist was done on a regular base by the majority of the respondents (61%).

Postoperative assessment

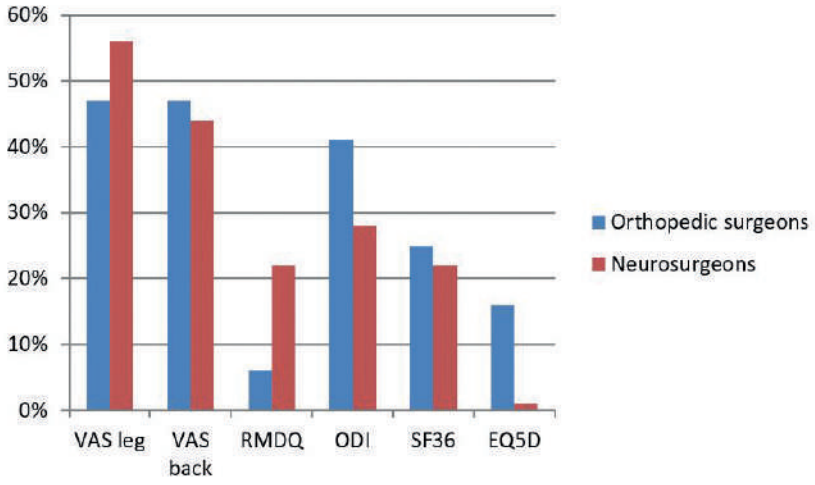
Radiographic assessment of lumbar fusion is listed in figure 4. The vast majority of surgeons assessed the result of fusion both radiologically and clinically (98%). 53% of surgeons assessed fusion after 1 year, 18% after 6 months and 14% after 3 months. The remaining 15% only evaluated the radiological fusion in case of persistent symptoms. There was no relation with clinical experience or case-load. In total, the most frequently used technique for imaging was plain radiographs (89% of all respondents). CT was used significantly more by neurosurgeons compared to orthopedic surgeons, 84% vs 31% respectively ($p<0.01$). Plain radiographs were used most by orthopedic surgeons (94%).

Figure 4. Standard radiographic assessment of spinal fusion



In order to measure the clinical outcome, most surgeons (62%) used validated questionnaires/patient related outcome measures (PROMs) (Figure 5). The Visual Analogue Scale (VAS) leg pain (52%) and VAS-back pain (48%) were the most used questionnaires. The Oswestry Disability Index (ODI) was the preferred questionnaire for measuring physical functioning (37% of respondents). There was a relation with clinical experience; surgeons with > 10 years of experience used PROMs significantly more frequently than surgeons with < 10 years of experience, 72% vs 43% respectively ($p=0.04$). There was no relation with case load ($p=0.12$). There were no significant differences between orthopedic surgeons and neurosurgeons ($p=0.48$).

Figure 5. Standard assessment of clinical outcome of spinal fusion by PROMs



Abbreviations used: PROMs = Patient Reported Outcome Measures, VAS = Visual Analogue Scale, RMDQ = Rolland Morris Disability Questionnaire, ODI = Oswestry Disability Index, SF36 = Short Form 36

DISCUSSION

In literature, the relation between disc degeneration on MRI and low back pain has been controversial. Although abnormal MRI findings in asymptomatic patients have been commonly observed (11), a large study conducted in 2009 demonstrated a significant association between lumbar disc degeneration on MRI and occurrence of low back pain symptoms (12). Pfirrmann et al described a validated T2-weighted MRI grading system for lumbar disc degeneration (10). Still, more than half (52%) of the respondents in our survey did not use this classification. Respondents who would regularly perform a spinal fusion on patients with SDD without radicular pain used the Pfirrmann score more often (64%). In 1988 Modic et al described several vertebral endplate signal changes (VESC) on MRI in patients with non-specific low back pain (13). The relationship between VESC, or Modic changes, on MRI and CLBP and disc degeneration has been shown by numerous studies (14, 15). However, a recently published randomized controlled trial (RCT) reported opposite results (16). Accordingly, about half (54%) of the respondents related Modic changes to

SDD. Respondents who would perform a spinal fusion on patients with SDD without radicular pain related Modic changes more often to SDD (86%).

Provocative discography is a controversial test due to unclear diagnostic accuracy, as it does not reliably predict the outcome of fusion (17). It may also cause degeneration of the disc (18). Therefore, the NASS does not recommend the use of discography to formulate treatment strategies for patients with low-back pain (19). Despite this, 42% of the respondents performed provocative discography and related recognizable pain with leakage of contrast to SDD.

The majority of the respondents (77%) preferred an interbody fusion technique, whereas 16% preferred PF/PLF. Although comparable in clinical outcomes, interbody fusion has been reported to be superior to posterolateral fusion in terms of higher fusion rates and better restoration of lumbar segmental and lordotic angle (20, 21). There are several studies that compared different interbody fusion techniques (22). However these are all underpowered studies. As reported by the updated guidelines of the NASS, no general recommendation can therefore be given (23).

Bone grafts alone instead of a cage lead to higher rates of collapse and pseudoarthrosis (24). Although use of cages for interbody fusion is common practice there is no consensus in literature on which type of cage should be preferred. Few studies have been published comparing different cage materials in lumbar surgery. No differences between PEEK and titanium cages regarding clinical and radiographic outcome were reported (25). In our survey the opinion was divided; most neurosurgeons preferred a PEEK cage (78%) whereas orthopedic surgeons preferred a titanium cage (34%).

Conflicting results are described concerning postoperative pain management. No difference in overall patient satisfaction with pain management, ambulation and length of stay was found between intravenous PCA and epidural PCA (26). However, other studies have described better pain management for epidural PCA with less side effects (27, 28). Therefore, a recommendation based on the literature could not be given. The vast majority of respondents in our survey favored intravenous PCA (79%).

NSAIDs have been associated with a higher risk for nonunion in patients undergoing spinal fusion (29, 29-31). NSAIDs are not superior to continuous subcutaneous and continuous epidural morphine for postoperative pain reduction perioperative (32). Still, about half (46%) of the respondents used NSAIDs after spinal surgery. Based on the literature we therefore advise against the use of NSAIDs.

In 2013 the NASS published an evidence based clinical guideline for the use of antibiotic prophylaxis in spine surgery (33). All of the respondents in our survey used prophylactic antibiotics during spinal surgery. There is insufficient evidence in the literature about the effect of single dose antibiotics versus prolonged antibiotic. Therefore no recommendations could be given.

In 2009 the NASS published an evidence based clinical guideline for the use of anti-thrombotic therapies in spine surgery (34). They recommended that pharmacological prophylaxis may be used postoperatively. However, these therapies should be considered on an individual case-by-case basis, as use may place patients at increased risk of bleeding complications (34). In our survey, only 37% of the respondents used venous thromboembolism (VTE) prophylaxis after spinal fusion, which were mainly orthopedic surgeons. This difference could be partly explained by their general acquaintance with the use of anticoagulants in joint-replacement surgeries. Based on the recommendations of the NASS, we suggest that VTE prophylaxis should be given perioperative to all spinal fusion patients unless they have a high risk of complications due to comorbidities. The length of prescription remains debatable.

There is insufficient evidence in literature about the use of a postoperative brace after interbody fusion or open vs less invasive procedures (35). The updated guidelines of the NASS do not recommend the use (36). In our survey 35% recommended the use postoperative, mainly by surgeons who reported to prefer an open procedure.

Bony fusion can be assessed by several radiographic techniques, including plain and dynamic radiographs, CT, MRI or bone scintigraphy. Plain radiographs are relatively cheap and easy to obtain with low radiation exposure. However, there are limitations: Static plain radiograph is only accurate in determining bony fusion in approximately two-thirds of the cases (37). CT scanning has a higher accuracy and thus, it has been

recommended to use plain radiograph in combination with CT scanning in case of persisting symptoms (38). This combination is also recommended by the NASS (39). Half of the respondents in our enquiry used CT scanning. The majority of the respondents (89%) used plain radiographs. 16% of the respondents assessed the radiological fusion only in case of clinical symptoms.

The use of PROMs are essential for comparing the effectiveness of different treatments (40). Several validated outcome measures are used, such as the VAS leg and VAS back pain, ODI, Roland Morris Disability Questionnaire (RMDQ) and Short Form 36 (SF36). However, in literature there is no consensus about which questionnaire should be used in standard clinical practice (4). Due to this it is very difficult to compare the outcome of different surgical techniques, implants and post-operative care. Therefore, the general use of selected questionnaires should be encouraged. Still, a large percentage of the respondents did not use any questionnaires in standard clinical practice (39%). The development of national registries with standard validated PROMs could help to gain more insight in the clinical outcome of patients. The NASS have recommended the use of the ODI and SF36 in their updated guidelines (40).

Referral to a physical therapist was done on a regular base by the majority of the respondents (61%). However, best clinical practice for physical therapy after a spinal fusion still remains unclear. A systematic review and meta-analysis evaluated the effectiveness of physical therapy following lumbar spinal fusion (41). The results were inconclusive. Also, timing of rehabilitation remains unclear (42). A large RCT about the effect of multidisciplinary cognitive-behavioral interventions for patients after spinal fusion was recently started (43).

Clinical relevance

The community has a need for uniform and consistent counseling, for which consensus in clinical practice is essential. The Nijmegen decision tool and the updated guidelines by the NASS are important steps in this process (8, 9). However, there is no consensus among spinal surgeons in the Netherlands regarding operative technique, type of instrumentation and cage material, postoperative management or radiological and clinical assessment in lumbar spinal fusion in patients with SDD.

Due to this patients are receiving a variety of treatments across the country with accompanying variety of possible long-term outcomes. Patient counseling prior to surgery is an important part of the surgeon's responsibility. Also, preoperative expectations are considered a major factor on the outcome of surgery (44). Since different surgical strategies result in different costs for surgery and post-operative care, third party-stakeholders such as policy makers and insurance companies ask for transparency and uniform treatment strategy.

In 2014 the Dutch Spine Surgery Registry (DSSR) started, in which surgeons are encouraged to enter their indications, operative strategies, type of materials and post-operative care of spinal fusions. Also, during follow-up patients are asked to fill in several validated PROMs (VAS leg and back pain, ODI, SF36, EQ-5D). This will allow the Dutch spinal community to create an overview of the general practice and monitor the effect of treatment and complications in clinical practice more closely. Together with the continued effort of the scientific community this may enable the installment of national guidelines for best practice in lumbar spinal care.

Limitations

This survey was conducted among DSS members and thus, the results may not be representative for all spine clinics. However, the vast majority of spine surgeons in the Netherlands that perform instrumented spinal fusion are a member of the DSS.

Conclusion

There is little consensus among spine surgeons in the Netherlands regarding perioperative management, type of instrumentation and cage material, operation technique, and postoperative management in lumbar spinal fusion in patients with symptomatic degenerative disc disorders, causing LBP. In society there is a growing demand for transparent uniform care. Therefore, the spinal community should put maximum effort in creating evidence based consensus guidelines for clinical practice.

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3

POLYETHERETHERKETONE (PEEK) CAGES IN CERVICAL APPLICATIONS: A SYSTEMATIC REVIEW

SPINE J 2015 JUN 1;15(6):1446-60

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ABSTRACT

Background context: PEEK cages have been widely used during the past decade in patients with degenerative disorders of the cervical spine. Their radiolucency and low elastic modulus make them attractive attributes for spinal fusion compared to titanium and bone graft. Still limitations are seen such as pseudoarthrosis and subsidence of the cages. Limited evidence on the clinical outcome of PEEK cages is found in the literature other than non-comparative cohort studies with only a few randomized controlled trials.

Purpose: To assess the clinical and radiographic outcome of PEEK cages in the treatment of degenerative disc disorders and/or spondylolisthesis in the cervical spine.

Study design: Systematic review of all randomized controlled trials, prospective and retrospective non-randomized comparative studies with a minimum follow-up of 6 months and all non-comparative cohort studies with a long-term follow-up of more than 5 years.

Outcome measures: The primary outcome variable was clinical performance. Secondary outcome variables consisted of radiographic scores.

Methods: The MEDLINE, EMBASE and COCHRANE LIBRARY databases were searched according to the PRISMA statement and MOOSE guidelines. No conflict of interest reported. No funding received.

Results: 223 studies were identified of which 10 studies were included. These comprised 2 randomized controlled trials, 5 prospective comparative trials and 3 retrospective comparative trials.

Conclusions: Minimal evidence for better clinical and radiographic outcome is found for PEEK cages compared to bone grafts in the cervical spine. No differences were found between PEEK, titanium and carbon fiber cages. Future studies should need to improve their methodology to minimize bias. Publication of lumbar interbody fusion studies needs to be promoted since differences in clinical and/or radiographic scores are more likely to be demonstrated in this part of the spine.

INTRODUCTION:

Chronic back pain is a major health problem and results in high socio-economic costs and loss of quality of life (1, 2). Degenerative disc disorders (DDD) are seen as an important source of pain (3, 4). DDD can initiate secondary changes leading to stenosis, spondylolisthesis and/or facet joint osteoarthritis. This may also lead to abnormal movement in the affected motion segment, which causes pain (3, 5, 6). Surgical stabilization of the degenerative segment by a bony fusion is a method to eliminate the pain. Some of the modern surgical techniques involve removal of the degenerated disk and placement of a graft in the intervertebral space in order to achieve interbody fusion through an anterior approach in the cervical spine or an anterior or posterior approach in the lumbar spine.

To promote interbody fusion of the affected segments autologous bone grafts were originally used. However, donor site morbidity, together with high failure rates resulting from collapse, subsidence, retropulsion or resorption of the graft with subsequent pseudoarthrosis or prolonged healing time were frequently seen (7-10). Therefore, interbody fusion cages were developed as an alternative for bone grafts (10). They are designed to contain a bone graft, allowing bony fusion through the cage between the adjacent vertebrae. Cages allow for direct axial load bearing and restoration of height of the intervertebral and foraminal space.

In 1988 Bagby introduced a stainless steel implant, which he used as a cage to promote spinal fusion and restore the disc height (11). This Bagby and Kuslich cage (BAK/C) showed good fusion rates (12). In the following years titanium alloy cages were commercialized. Although high fusion rates and good clinical improvement scores were reported (13-15) , these cages still had some disadvantages. For instance, subsidence is still seen in high percentages, varying from 16% to 60% (16-19). Furthermore, titanium is radio-opaque which makes it difficult to visualize bone formation on radiograms after implantation.

To improve visualization of bone formation, radiolucent cages have been developed. Examples of these are resorbable poly(L-lactide-co-D, L-lactide) (PLDLLA) (20) and carbon fiber cages (21). However, subsidence and pseudoarthrosis are still seen with

these types of cages. One-third of patients with PLDLLA cages actually showed a 10% worsening of Visual Analog Score (VAS) and Oswestry Disability Index (ODI) scores. Also, signs of osteolyses were seen in the PLDLLA treatment group (20).

Polyetheretherketone (PEEK) cages became available during the late 1990`s. They reduce stress shielding because of their lower elastic modulus compared to titanium (22, 23). Radio-opaque markers are present to visualize PEEK cages. They cause less artifacts on CT and MR scans as compared to titanium and allow visualization of bony fusion.

Historical background:

PEEK materials have been commercialized in the 1980s and belong to the family of polyaryletherketone (PAEK) polymers (24). PEEK has the ability to withstand high temperatures (up to 300 degrees Celsius) and is resistant to chemicals and radiation. PEEK is compatible with reinforcing agents and has great strength exceeding many metals (25, 26). Originally used in industrial applications, PEEK was explored as a biomaterial in prosthetic implants during the 1980s (27, 28). It wasn't until the late 1990s that PEEK was offered commercially as a biomaterial for spinal cages (22). The first composites consisted of carbon-fiber reinforced polyetherketoketherketonketon (PEKEKK) and showed positive biomechanical results in a cadaveric cervical and lumbar study (29). In this study, the PEKEKK implant was compared with allograft human bone blocks of the proximal femur. Compression tests showed the PEKEKK implant had a similar compressive strength as the highest quality of bone implant, and the pullout resistance of the PEKEKK implant exceeded those of the allograft. Next to this, an animal study was performed in which Spanish goats received either a PEKEKK cage with autologous iliac crest graft (CFRP cage) or allograft bone blocks (30). At 6 and 12 months higher histological and radiographic fusion rates were seen for CFRP cages compared to allograft. Furthermore, the cage was clinically evaluated in a FDA approved prospective multicentre study in 221 patients (31). All patients underwent a lumbar interbody fusion with the carbon-fiber reinforced PEKEKK cage filled with autologous graft, followed by posterior fixation with pedicle screws and plates. At 24 months, 98.6% of patients who had 2-year radiographic evaluation (178 patients) achieved fusion. In 13.5% of patients there were minor device-related complications, of which broken pedicle screws were the majority.

There were 10.4% major non-device related complications, 8 deep wound infections required reoperation. Further surgery was performed in 46.1% (102 patients) due to elective removal of screws and plates (35.2%), to address new disc levels or to repair dural tears. 5 Out of 221 patients (2.2%) needed revision of the pedicle screws or cages. The lumbar carbon-reinforced PEKEKK cage came to be known as the Brantigan cage (22). Carbon-fiber reinforced PEKEKK cages were however abandoned by their industrial supplier for reasons that are not well documented in literature, and thus ceased to exist (22). This laid the foundation to the current use of PEEK cages.

PEEK cages have been widely used during the past decade (22, 32-34). Their radiolucency and low elastic modulus make them attractive attributes for spinal fusion (35). Still drawbacks are seen such as subsidence and migration of the cages (36-38). PEEK has a hydrophobic surface, which allows neither protein absorption nor promotes cell adhesion (39). An animal study has reported that PEEK cages are encapsulated by a thin fibrous tissue layer (40). Theoretically this can interfere with the host-bone integration, which may lead to subsidence and migration. Other than elastic modulus, different design factors are likely to play a large role determining the overall performance of an interbody implant (35). A radiolucent cage could contribute to difficulties in visualization during surgery, whereas radio-opaque cages such as titanium are visible while using fluoroscopy. Despite this, PEEK cages have become more popular over the last few years.

Limited evidence on the clinical outcome of PEEK cages is found in the literature other than non-comparative cohort studies with only a few randomized controlled trials (RCT's). Therefore, in this study we systematically reviewed the available literature on the clinical and radiographic outcome of PEEK cages compared to other interbody cages.

Since only a limited number of lumbar interbody fusion studies were found in literature, with large variation in operative techniques and indications for surgery, only cervical interbody fusion studies were included in our review.

METHODS

Objectives:

The objective of this systematic review was to assess the clinical and radiographic outcome of all clinical comparative and long-term non-comparative cohort studies of PEEK cages in the treatment of degenerative disc disorders and/or spondylolisthesis in the cervical spine.

Search strategy

A systematic literature search was performed by the first author on October 5th 2012. The MEDLINE, EMBASE and COCHRANE LIBRARY databases were used according to the PRISMA statement (41) and MOOSE guidelines (42). The advanced search strategy consisted of a combination of keywords combined with synonyms. The first part of the syntax was build up from the term 'PEEK' combined with synonyms using 'OR'. The second part was build up from the term 'Spine' combined with synonyms using 'OR'. The last part was build up from the term 'Cage' combined with synonyms using 'OR'. The final syntax combined the results of the three searches using 'AND'. No MESH terms were used. The precise syntax used on October 5th 2012 was: (((((((PEEK) OR polyetheretherketone) OR polyether-ether-ketone) OR poly-ether-ether-ketone)) AND ((((Spine) OR spinal) OR interbody) OR vertebral))) AND (((cage) OR spacer) OR implant).

Types of study

RCT's and prospective or retrospective comparative clinical trials with a follow-up of at least 6 months were included. A minimal of 10 patients per treatment arm was deemed necessary. Additionally, to analyze the long-term outcome of PEEK cages, non-comparative cohort studies with a follow-up of at least 5 years were also included.

Types of interventions

Studies analyzing interbody fusion techniques with PEEK cages in the cervical spine in patients with degenerative disc disorders and/or spondylolisthesis were included. Trials including patients with infections, tumors, scoliosis and/or fractures were excluded.

Types of outcome measures

The required outcome variables were both clinical performance and radiographic outcome. Primary outcome variable was the clinical performance. The mean clinical important difference (MCID) of each primary outcome variable was obtained, and was subsequently compared to the results of each included study. If no evidence of the MCID of a primary outcome variable could be found, a 30% improvement rate from baseline was chosen as the MCID as suggested by Ostelo et al (43). Improvement scores exceeding the range of the MCID were considered to be clinically relevant. Secondary outcome variables consisted of radiographic scores. Expected primary and secondary outcome variables are listed below, however no exclusions were made on the type of outcome variables.

Clinical performance (primary outcomes):

- Visual Analog Scale (VAS) (44)
- Oswestry Disability Index (ODI) (45)
- Neck Disability Index (NDI) (46)
- Japanese Orthopedic Association score (JOA-score) (47)
- ODOM`s criteria (48)
- Patients satisfaction by Likert Scale (49)
- Prolo scale (50)
- SF36 (51-53)

Radiographic scores (secondary outcomes):

- Fusion
- Foraminal height
- Disc height
- Lordosis
- Subsidence
- Migration

Study selection

The search was limited to the English, Dutch and German languages. The search results were exported to an online Refworks database (RefWorks 2.0). All duplicates were identified and subsequently removed from the database. All studies were screened by title and abstract. Full text was retrieved from all studies that met the inclusion criteria. Multiple evaluations

of a single cohort were excluded, only the longest follow-up was included. Full text was subsequently screened for exclusion criteria. Table 1 lists the inclusion and exclusion criteria.

Table 1: Inclusion and exclusion criteria

Inclusion:	- Intervertebral PEEK cage application - Degenerative disc disorders and/or spondylolysis/listhesis - Comparative clinical study with FU > 6 months - Non-comparative clinical study with FU > 5 years - Written in English, German or Dutch
Exclusion:	- Biomechanical, animal or in-vitro studies - Reply/commentary on a study - Full article not available - Revision surgery - Spondylodiscitis - Vertebral tumors - Vertebral fracture - Scoliosis - < 10 patients per treatment arm - Thoracic and/or lumbar fusion studies

Quality Assessment

The risk of bias was assessed by two of the authors (RK, SvG). Potential disagreement was resolved by consensus. Risk of bias of randomized controlled trials was assessed by the checklist recommended by the Cochrane Back Research Group (54). The risk of bias of non-randomized comparative studies was assessed by the criteria of the Newcastle – Ottawa quality assessment scale (55). Risk of bias was considered low if studies met at least 50% of the items of the Cochrane Back Research Groups checklist or the Newcastle-Ottawa quality assessment scale. All low risk of bias studies were considered best evidence and were included in our review. Non-comparative cohort studies with a follow-up of at least 5 years were also considered to be at low risk of bias and therefore included in our study. Furthermore, the level of evidence for each study was determined (56, 57).

Data Extraction

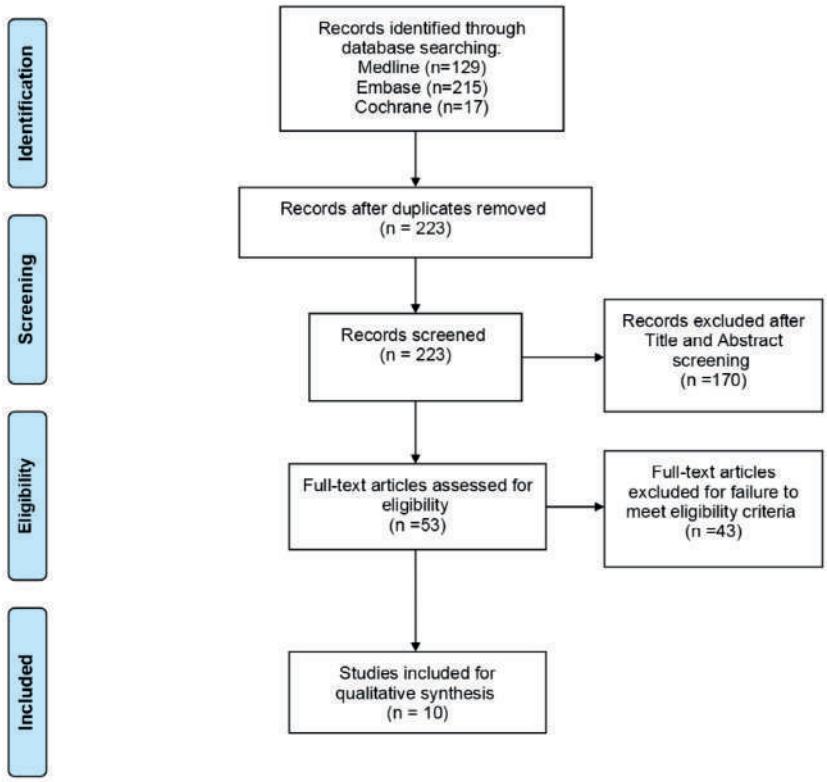
Primary and secondary outcome variables of the selected studies were recorded on pre-developed forms in Excel (Microsoft Office 2003). Also, basic information on study design, indications for surgery, operative technique, age, sex and complications were recorded. Outcome variables of the included studies are presented in tables 2, 3 and 4.

RESULTS

Search and selection

A systematic search of the Medline, Embase and Cochrane databases identified 223 articles, excluding duplicates. After screening title and abstract by two of the authors (RK, SvG), a total of 53 articles met the inclusion criteria. After reading full text, 39 articles were excluded based on the exclusion criteria. Of the 14 selected articles, 4 articles evaluated PEEK cages after lumbar interbody fusion and were also excluded. Finally, a total of 10 studies were included. A cross-reference check of the included studies revealed no new studies. A flow diagram is provided in figure 1.

Figure 1: PRISMA flow diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Types of studies

Two RCT's, five prospective comparative trials and three retrospective comparative trials were identified. (Non)-comparative studies with a long-term follow-up of more than 5 years were not identified. One RCT compared PEEK cages packed with autograft to autologous iliac crest graft (AICG) in patients after anterior cervical decompression and fusion (ACDF) (58). A second RCT evaluated titanium vs. PEEK cages after ACDF (14).

Sponsorship

1 out of 10 studies reported connections with industry. 1 Out of 10 studies received funding from research grants. 4 Out of 10 studies specifically reported no funding was received. In the remaining studies potential conflict of interests was not discussed.

OUTCOMES

PEEK cage versus human bone graft

A prospective RCT by Celik et al (58) evaluated the differences in cervical foraminal height changes between stand-alone PEEK cages in 35 patients on 41 levels in total (29 one-level, 6 two-level) AICG in 30 patients on 46 levels in total (14 one-level, 16 two-level) after ACDF. Indication for surgery was radiculopathy. Clinical outcome was measured by the VAS score and the JOA myelopathy scoring system. Radiographic outcome was performed by radiogram at the 1st, 3rd, 6th, 12th and 18th month postoperatively. No significant differences were seen in the clinical outcomes and time of hospital stay between the two groups during follow-up. After radiographic analysis, the foraminal height directly postoperative significantly improved in the PEEK group compared to preoperative, which was maintained during follow-up. In the graft group the foraminal height directly postoperative significantly improved compared to preoperative. However, this correction was not maintained at the 6th, 12th and 18th month interval. Direct postoperative, significant improvements in disc height were found in the PEEK group, which was maintained during follow-up. In the graft group a significant increase in disc height was found directly postoperative, however this was not maintained during the 3rd, 6th, 12th and 18th month interval. There was no difference in cervical lordosis in both groups. No subsidence was seen in the

PEEK group, whereas in the graft group, 19 levels in 13 patients exhibited subsidence (43.3%). All were observed between the 1-6 months interval. Differences between one-level and two-level surgery patients were not described. They conclude that the PEEK cage is superior to iliac graft in increasing and preserving the foraminal and disc height for up to 18 months. However, this preservation does not relate to clinical recovery in any way.

Cho et al published a prospective study on the use of PEEK cages in ACDF (59). 40 Patients underwent stand-alone fusion with the PEEK cage packed with autograft on 66 levels in total (22 one-level, 10 two-level, 8 three-level). Another group of 40 patients were treated with stand-alone AICG on 58 levels in total (20 one-level, 12 two-level, 8 three-level). Indications for surgery were radiculopathy (PEEK 18, AICG 18), myelopathy (PEEK 12, AICG 10) and radiculo-myelopathy (PEEK 10, AICG 12). Patients were not randomized. Follow-up was 6 months. Clinical outcome was measured with the PROLO score. Radiographic follow up was performed by radiogram. At 6 months, PROLO scores were significantly higher in the PEEK group as compared to the graft group (8.5 ± 1.5 vs. 7.2 ± 2.1). No differences were seen in hospital stay between the two groups. After radiographic analysis, foraminal heights were significantly improved in the PEEK group as compared to pre-operative values. No differences were found in the graft group post-operative. Segmental cervical lordosis significantly increased in the PEEK cage as compared to pre-operative values. No difference was found in the graft group post-operative. Both groups showed good fusion results (100% in PEEK vs. 93% in AICG). A 10% graft collapse rate was found in the graft group. Dislodgement of grafts was found in 5% of the cases. No complications were seen in the PEEK group. Differences between one-level, two-level and three-level surgery patients were not described. Also, differences between indications for surgery were not described. They conclude the PEEK cage is a good substitute for ACDF with AICG in patients with cervical disc disease.

Vanek et al (60) compared three ACDF techniques in a prospective study: stand-alone autograft (Group 1, 28 patients; 20 one-level, 8 two-level), autograft with anterior plate fixation (Group 2, 18 patients; 9 one-level, 9 two-level) and PEEK cage filled with beta-tricalcium phosphate and anterior plate fixation (Group 3, 29 patients; 14 one-level, 15 two-level). Indication for surgery was radiculopathy. Patients were

not randomized. The follow-up was 2 years. Clinical outcome was evaluated by the VAS, NDI and the modified Odom's criteria to monitor the satisfaction rate after surgery. Radiographic follow-up was performed by plane radiograms. No significant differences were found in NDI and VAS. Satisfaction rate in group 1 after 2 years was significantly lower than in the other 2 groups ($p=0.03$). No differences in satisfaction rate were found between one-level and two-level surgery patients. Fusion rate was 100% in all three groups. Relative segmental height in group 1 was significantly lower since the 6th week postoperatively compared with the other groups ($p<0.01$). Significantly lower values of lordosis were found in group 1 compared with the other 2 groups. Three reoperations were indicated in group 1 due to symptomatic graft collapse or anterior migration within the first 2 months and were further excluded from the study. The other groups had no indications for re-operations. They conclude anterior plating seems to be an important factor influencing the postoperative cervical alignment and clinical outcomes. PEEK cages filled with artificial substrate and plating can offer similar results as iliac autograft with plating.

The research group of Vaidya et al (61) performed a retrospective non-randomized study in patients undergoing anterior cervical fusion supplemented with an anterior locking plate. PEEK cages filled with recombinant human bone morphogenetic protein-2 (rhBMP-2) in 22 patients at 38 levels in total (8 one-level, 9 two-level, 4 three-level) were compared to allograft spacers with demineralized bone matrix in 24 patients at 40 levels in total (11 one-level, 10 two-level, 3 three-level). Indications for surgery were radiculopathy (PEEK 19, Allograft 20) or radiculo-myelopathy (PEEK 3, Allograft 4). Follow-up was performed at 2 and 6 weeks, 3, 6 and 12 months and at latest follow-up. Clinical outcome was measured with the VAS and cervical ODI scores. Radiographic follow-up was performed by radiogram. Clinical scores showed significant improvement from base-line at follow-up with no differences found between the groups. Successful fusion rates were found after one year (100% PEEK vs. 97.5% allograft). End plate resorption in all levels of the PEEK group with rhBMP-2 was seen between 6 weeks and 6 months after surgery. Additionally, significantly more patients with dysphagia were seen in the PEEK with rhBMP-2 group. In two and three-level patients there was significantly less dysphagia in the allograft group at 6 weeks ($p=0.02$). The incidence of dysphagia in single-level patients in the PEEK group was higher compared to the allograft group at 2 weeks (71% vs. 13%).

However, this difference was not statistically significant (p=0.07). Furthermore, total costs of the PEEK with rhBMP-2 group were more than three times higher than in the allograft group. Differences between indications for surgery were not described. Based on these results, Vaidya et al have abandoned using rhBMP-2 and PEEK cages for anterior cervical fusion.

A prospective study by Zhou et al (62) compared the use of stand-alone PEEK cages packed with autograft in 40 patients at 64 levels in total (30 one-level, 17 two-level) to AICG combined with plate fixation in 32 patients at 51 levels in total (21 one-level, 15 two-level) in ACDF. Indications for surgery were radiculopathy (PEEK 29, AICG 22) and myelopathy (PEEK 11, AICG 10). Patients were not randomized. Follow-up was 12 months. Clinical outcome was measured with the JOA score. Radiographic follow-up was performed by radiogram and CT. JOA scores showed no significant differences between the two groups. Differences between one-level and two-level patients were not described. Operative time and blood loss in the PEEK group were significantly lower than the AICG group for both one-level and two-level patients ($p<0.05$). All patients in both groups achieved complete fusion. In both groups a significant increase in disc height was found directly postoperative, which maintained during follow-up. Also a significant increase in lordosis was found in both groups directly postoperative, which was maintained during follow-up. No differences were found between the groups. Radiographic differences between one-level and two-level patients were not described. Furthermore, differences between indications for surgery were not described. They conclude that stand-alone PEEK cages packed with autograft are a good alternative in the treatment of patients with cervical disc disease.

Lied et al (63) examined the clinical outcome of ACDF in patients treated with either a stand-alone PEEK cage (n=77) or AICG (n=181). Levels operated per procedure were not specified between treatment groups. In total there were 152 one-level, 104 two-level and 2 three-level surgery patients. Indications for surgery were also not specified between treatment groups. Indications for surgery were radiculopathy (206 patients), myelopathy (9 patients), radiculo-myelopathy (36 patients) and 7 patients with no signs of radiculopathy or myelopathy. Patients were not randomized. Follow-up was 6 months. Clinical outcome was evaluated by VAS arm and neck scores. At follow-up, both groups showed a significant improvement but no differences were

found between the two groups. Differences between one-level, two-level and three-level patients were not described. Also, differences between indications for surgery were not described. The authors conclude that the PEEK cage is preferred to AICG based on the absence of donor site morbidity combined with shorter operation time.

A retrospective study by Sethi et al (64) analyzed the radiographic changes in cervical and lumbar interbody fusion using either allograft + rhBMP-2 or PEEK cages + rhBMP-2. Only the results of the cervical group will be presented here. Patients were not randomized. Radiographic follow-up was performed by radiogram. Cervical patients underwent ACDF with anterior plate fixation. A PEEK cage was used in 23 patients, allograft was used in 11 patients at 50 levels in total. Levels operated per procedure were not specified between treatment groups. Indications for surgery were also not specified. After 6 months the fusion rate of the PEEK group was higher (91% vs. 81%). One patient in the PEEK group displayed cage migration. No migration was observed in patients treated with allograft. Subsidence was seen in more than 50% of the entire population. Endplate resorption was seen in 82% of all cervical patients. The authors conclude that rhBMP-2 causes subsidence, end-plate resorption and cage migration.

Table 2. Peek versus bone grafts

Author	Level of evidence	Design	Tech	N	Mean FU (months)	Clinical outcome	Fusion rate (%)	Complication	Lordotic angle (°)	Interspace height (mm)
Celik et al, 2007 (58)	Level II	RCT	ACDF	- 35 PEEK + autograft (29 one-level, 6 two-level) - 30 AICG (14 one-level, 16 two-level). Indication for surgery: - Radiculopathy	18	VAS arm improvement (0-10 scale): preop 7.1 vs 7.1. FU 0.2 (0.4) vs. 0.3 (0.2) VAS neck improvement (0-10 scale): preop 8.0 vs 8.4. FU 0.3 (0.2) vs. 0.2 (0.4) JOA improvement: preop 2.3 vs. 1.9. FU 15.8 (0.7) vs. 15.3 (1.1) MCID: VAS arm: 2.5 - 4.1 (66, 67) VAS neck: 2.5 - 2.6 (66, 67) JOA: 30% improvement from baseline (43)	-	Subsidence: 0% vs. 43.3% *	PEEK preop 12.1 (3.6), direct post 13.3 (3.1), FU 12.6 (3.2) AICG preop 11.7 (4.5), direct postop 12.7 (4.4) FU 11.8 (3.8)	Disc height: - PEEK preop 3.4 (1.8), direct postop 5.6 (0.3) *, FU 4.5 (1.2) * - AICG preop 3.1 (1.7),direct postop 5.8 (1.6) *, FU 2.6 (1.7) Foraminal height: - PEEK preop 8.4 (2.8), direct postop 10.3 (1.1) *, FU 9.6 (1.2) * - AICG preop 8.2 (2.7),direct postop 10.8 (2.6) *, FU 8.1 (1.5)
Cho et al, 2002 (59)	Level II	Prospective.	ACDF Stand-alone	- 40 PEEK + autograft (22 one-level, 10 two-level, 8 three -level) - 40 AICG (20 one-level, 12 two-level, 8 three-level) Indication for surgery: - Radiculopathy (PEEK 18, AICG 18) - Myelopathy (PEEK 12, AICG 10) - Radiculo-myelopathy (PEEK 10, AICG 12)	6	PROLO FU: 8.5 (1,5) vs. 7.2 (2,1) * MCID: PROLO: 30% improvement from baseline (43)	PEEK 100% vs. AICG 93.1%	Graft collaps: 0 vs. 10% Graft dislodgment: 0 vs. 5%	PEEK preop 3.8 (4.5), FU 6.2 (5.5), mean increase 2.3 (1.4) * AICG preop 5.9 (5.9), FU 4.8 (6.7), mean decrease 0.8 (6.7)	Foraminal height: - PEEK preop 8.8 (1.8), FU 11.7 (1.8).* - AICG: preop 10.1 (2.2), FU 10.9 (2.6).

Table 2. Peek versus bone grafts (continued)

Author	Level of evidence	Design	Tech	N	Mean FU (months)	Clinical outcome	Fusion rate (%)	Complication	Lordotic angle (°)	Interspace height (mm)
Vanek et al, 2012 (60)	Level II	Prospect.	ACDF	- 28 autograft (20 one-level, 8 two-level) - 18 autograft + plate (9 one-level, 9 two-level) - 29 PEEK + plate + beta tricalcium phosphate (14 one-level, 15 two-level) Indication for surgery: - Radiculopathy	24	NDI improvement: graft 27.2 (15.1), graft + plate 23.7 (11.3), PEEK 18.2 (11.6). No difference between groups VAS improvement (0-10 scale): graft 6.9 (1.2), graft + plate 6.9 (0.7), PEEK 7.3 (1.0). No diff between groups Modified ODOM: autograft most unsatisfied vs. others*. No difference between one-level and two-level MCID: NDI: 7.5 – 10.5 (66, 68) VAS: 1.5 – 2.5 (43, 66) ODOM: not available	100% vs. 100% vs. 100%	Autograft: 3 reoperations for graft collaps or migration. No other complications	Autograft Group: lower values than other 2 groups *	Disc Height: - Autograft: 95% preop vs. postop - Autograft + plate: 105% preop vs postop - PEEK + plate: 105% preop vs. FU
Vaidya et al, 2007 (61)	Level III	Retrospt.	ACDF	- 22 PEEK + rhBMP`s + plate (8 one-level, 9 two-level, 4 three-level) - 24 allograft + demineralixed bone + plate (11 one-level, 10 two-level, 3 three-level). Indication for surgery: - Radiculopathy (PEEK 19, Allograft 20) - Radiculo-myelopathy (PEEK 3, Allograft 4)	12	VAS arm (0-10 scale): PEEK preop 5.0, FU 1.3 *. Allograft preop 7.1, FU 1.8 *. No diff between groups VAS neck (0-10 scale): PEEK preop 7.1, FU 2.6 *. Allograft preop 8.5, FU 2.6 *. No diff between groups ODI: PEEK preop 53.3, FU 28.8 *. Allograft preop 60.4, FU 27.1 *. No diff between groups MCID: VAS arm: 2.5 - 4.1 (66, 67) VAS neck: 2.5 - 2.6 (66, 67) ODI: 10 (43)	PEEK 100% vs. Allograft 96%	Endplate resorption in 100% of PEEK (+ rhBMP`s). Dysphagia: more in PEEK + rhBMP`s at 2 and 6 wks* More in multi-level PEEK + rhBMP`s at 6 weeks*		-

Table 2. Peek versus bone grafts (continued)

Author	Level of evidence	Design	Tech	N	Mean FU (months)	Clinical outcome	Fusion rate (%)	Complication	Lordotic angle (°)	Interspace height (mm)
Zhou et al, 2011 (62)	Level II	Prospect.	ACDF Stand-alone	- 40 PEEK + autograft (30 one-level, 17 two-level) - 32 AICG (21 one-level, 15 two-level) Indications for surgery: - Radiculopathy (PEEK 29, AICG 22) - Myelopathy (PEEK 11, AICG 10)	12	JOA recovery rate: 93.4% vs. 92.1% MCID: JOA: 30% improvement from baseline (43)	100% vs. 100%	Operative time lower in PEEK for both one-level and two-level *	PEEK preop 3.9 (0.9), directly postop 8.9 (0.9)* FU 8.8 (1.0) *. AICG preop 3.8 (0.8), directly postop 8.6 (0.9) *, FU 8.4 (0.8) *. No diff between groups	Disc height: - PEEK preop 5.9 (0.5), directly postop 8.7 (0.9) *,FU 8.6 (0.9) * - AICG preop 5.6 (0.5),directly postop 8.2 (0.7)*, FU 8.1 (0.7) * - No diff between groups
Lied et al, 2010 (63)	Level II	Prospect.	ACDF Stand-alone	- 77 PEEK - 181 AICG Levels not specified per group. In total one-level (152), two-level (104), three-level (2). Indications for surgery: - Radiculopathy (206 in total) - Myelopathy (9 in total) - Radiculo-myelopathy (36 in total) - No radiculopathy or myelopathy (7 in total)	6	VAS arm improvement (0-10 scale): Total population 3.05 No diff between groups. VAS neck improvement (0-10 scale): Total population 2.30 No diff between groups MCID: VAS arm: 2.5 - 4.1 (66, 67) VAS neck: 2.5 - 2.6 (66, 67)	-	Operative time + donor site morbidity lower in PEEK group	-	-
Sethi et al, 2011 (64)	Level III	Retrospt.	ACDF	- 23 PEEK + rhBMP`s + plate - 11 allograft + rhBMP`s + plate Levels not specified per group. In total 50 levels. Indications for surgery not specified	ACDF: 6	-	PEEK 91% vs. Allograft 81%	Subsidence: Total population 16.5% at FU Cage migration: 1 PEEK, Allograft no subsidence	-	-

Abbreviations used: PEEK = polyetheretherketone; FU = follow-up; RCT = randomised controlled trial; ACDF = anterior cervical discectomy and fusion; AICG = autologous iliac crest graft; VAS = Visual Analogue Scale; JOA = Japanese Orthopaedic Association score; MCID = minimal clinical important difference; * = significantly different from preoperative data; PROLO = Prolo scale; NDI = Neck Disability Index; ODOM = Odom`s criteria; rhBMP = recombinant human bone morphogenetic protein-2; ODI = cervical Oswestry Disability Index

PEEK cage versus Titanium cage:

A RCT by Niu et al (14) compared the amount of fusion 1 year after ACDF without anterior plate fixation. In 25 patients a PEEK cage filled with allograft was used at 34 levels in total (16 one-level, 9 two-level). In 28 patients a titanium cage (Ti) filled with autograft and calcium phosphate bone substitute was used at 37 levels in total (19 one-level, 9 two-level). Indications for surgery were radiculopathy (PEEK 19, Ti 21), myelopathy (PEEK 3, Ti 3) and radiculo-myelopathy (PEEK 3, Ti 4). Clinical outcome was evaluated by ODOM`s criteria. Radiographic analysis was measured by radiogram. Follow-up was 12 months. Hospital stay and estimated blood loss did not differ between the two groups, however mean operation time was longer in the PEEK group ($p=0.02$). The ODOM criteria showed no significant differences between the two groups at follow-up. Total amount of fusion in the PEEK group was 100%, compared to 86.5% in the titanium group ($p=0.03$). Directly postoperative, similar improvements in the lordotic angle and disc height were seen in both groups. However, in the titanium group there was a larger decrease in correction of lordotic angle and disc height during follow-up compared to the PEEK group. Significantly higher amounts of subsidence were found in the titanium group than in the PEEK group (titanium 16.2% vs. PEEK 0%, $p<0.01$). Differences between one-level and two-level patients were not described. Also, differences between indications for surgery were not described. Based on these results, the authors prefer the use of PEEK cages with allograft as an interbody spacer for ACDF.

A retrospective study by Cabraja et al (65) compared the results in patients who underwent one-level ACDF with a stand-alone PEEK cage (42 patients) or titanium cage (44 patients). No cage filling was used. Indications for surgery were radiculopathy (PEEK 34, Ti 36) and myelopathy (PEEK 8, Ti 8). The authors hypothesized that the titanium cage could show more subsidence and lower fusion rates based on the higher modulus of elasticity compared to the PEEK cage. Follow-up was 28 months. Clinical outcomes were measured by the ODOM criteria, VAS and NDI. Radiographic measurements were performed by radiogram. A similar increase in all clinical scores was reported in both groups. Also, no differences were found in fusion rate (PEEK 88.1% vs. titanium 93.2%), subsidence (PEEK 14.3% vs. titanium20.5%) and cervical lordosis directly postoperative and during follow-up. Differences between indications for surgery were not described. The authors conclude the modulus of elasticity represents only one of many characteristics of a cage, and other factors need to be considered.

Meier et al (13) compared the use of 6 different interbody spacers in a prospective study. Patients underwent a stand-alone ACDF. 60 Patients received a PEEK cage (39 One-level, 21 two-level), 190 patients received 4 different titanium cages in total (140 one-level, 48 two-level, 2 three-level). Indications for surgery were radiculopathy or myelopathy (not specified). After 12 months, no differences were found in recovery rate. The authors describe a tendency for dislocation of the PEEK cage and a tendency for subsidence of the titanium cages. Differences between one-level, two-level and three-level patients were not described.

Table 3. PEEK versus titanium

Author	Level of evidence	Design	Tech	N	Mean FU (months)	Clinical outcome	Fusion rate (%)	Complication	Lordotic angle (°)	Interspace height (mm)
Niu et al, 2010 (14)	Level II	RCT	ACDF Stand-alone	- 25 PEEK + allograft (16 one-level, 9 two-level) - 28 Ti + autograft + calcium phosphate (19 one-level, 9 two-level) Indications for surgery: Radiculopathy (PEEK 19, Ti 21) Myelopathy (PEEK 3, Ti 3) Radiculo-myelopathy (PEEK 3, Ti 4)	12	ODOM: Excellent / good: PEEK 80% vs. Ti 75% MCID: ODOM: not available	100% vs. 86.5%*	Collaps > 3mm: PEEK 0% vs. Ti 16.2%*	PEEK preop 2.2 (4.9), direct postop 6.9 (5.2), FU 4.0 (5.7) Ti preop 1.6 (3.6), direct postop 6.6 (3.9), FU 3.3 (4.2). No difference between groups Loss of lordosis at FU: PEEK 3.2 (2.4), Ti 2.8 (3.4). No diff	Anterior disc height: PEEK preop: 5.3 (1.3), direct postop 6.5 (1.0), FU 6.0 (1.0) Ti preop 5.2 (1.3), direct postop 8.6 (1.2), FU 7.0 (1.5) Posterior disc height: PEEK: preop 5.2 (1.4), direct postop 6.1 (1.0), FU 5.6 (1.2) Ti preop: 4.6 (0.8), direct postop 6.1 (0.8), FU 4.5 (0.9) Loss of correction at FU: PEEK 0.5 (0.5), Ti 1.6 (0.9) *
Cabraja et al, 2012 (65)	Level III	Retrospt.	ACDF Stand-alone	- 42 PEEK (one-level) - 44 Ti (one-level). No cage fillings used Indications for surgery: Radiculopathy (PEEK 43, Ti 36) Myelopathy (PEEK 8, Ti 8)	28	ODOM: Excellent/good PEEK 75% vs. Ti 64.3% VAS arm FU (0-100 scale): PEEK 25.8 (26.7) vs. Ti 23.7 (23.8) VAS neck FU (0-100 scale): PEEK 36.3 (21.3) vs. Ti 33.0 (18.5) NDI FU: PEEK 17.0 (9.6) vs. Ti 16.9 (10.2) MCID: ODOM: not available VAS arm: 2.5 - 4.1 (66, 67) VAS neck: 2.5 - 2.6 (66, 67) NDI: 7.5 – 10.5 (66, 68)	PEEK 88.1% vs Ti 93.2%	Subsidence: PEEK 14.3% (2.9 ±0.6) vs Ti 20.5% (3.1±0.3)	Operated segment: PEEK preop 4.4(3.4), direct postop 6.5(3.7)*, FU 5.5(4.1)* Ti preop 2.7 (4.7), direct postop 5.5(3.9)*, FU 4.1 (3.7)* Cervical lordosis: PEEK preop 16.3 (11.2), direct postop 17.6 (10.0)*, FU 13.3 (7.1) Ti preop 10.8(14.5), direct postop 14.0(12.4)*, FU 13.1 (12.7)	-

Table 3. PEEK versus titanium (continued)

Author	Level of evidence	Design	Tech	N	Mean FU (months)	Clinical outcome	Fusion rate (%)	Complication	Lordotic angle (°)	Interspace height (mm)
Meier et al, 2004 (13)	Level II	Prospect.	ACDF Stand-alone	- 60 PEEK (39 One-level, 21 two-level) - 190 Ti (140 one-level, 48 two-level, 2 three-level). In total 4 different Ti cages used Indications for surgery (not specified): Radiculopathy Myelopathy	12	No differerence in recovery rate	-	PEEK: tendency for dislocation Ti: tendency for subsidence	-	-

Abbreviations used: PEEK = polyetheretherketone; FU = follow-up; RCT = randomised controlled trial; ACDF = anterior cervical discectomy and fusion; Ti= titanium; ODOM = Odom`s criteria; MCID = minimal clinical important difference; * = significantly different from preoperative data; VAS = Visual Analogue Scale; NDI = Neck Disability Index

PEEK cage vs. carbon fiber cages:

In the same study Meier et al (13) also compared the PEEK cage in 60 patients (39 One-level, 21 two-level) with a carbon fiber cage in 17 patients (11 one level, 6 two-level). All patients underwent a stand-alone ACDF. Indications for surgery were radiculopathy or myelopathy (not specified). After 12 months, no differences were found in recovery rate. However, the authors describe a tendency for subsidence of the carbon fiber cage. Also, the costs of the carbon fiber cage are higher. Differences between one-level, two-level and three-level patients were not described.

Table 4. PEEK versus carbon fiber

Author	Level of evidence	Design	Tech	N	Mean FU (months)	Clinical outcome	Fusion rate (%)	Complication	Lordotic angle (°)	Interspace height (mm)
Meier et al, 2004 (13)	Level II	Prospect.	ACDF Stand-alone	- 60 PEEK (39 One-level, 21 two-level) - 17 carbon fiber (11 one-level, 6 two-level) Indications for surgery (not specified): Radiculopathy Myelopathy	12	No difference in recovery rate	-	PEEK: tendency for dislocation Carbon fiber: more expensive (270 euro PEEK vs 450 euro Carbon Fiber)	-	-

Abbreviations used: PEEK = polyetheretherketone; FU = follow-up; ACDF = anterior cervical discectomy and fusion

Discussion

Clinical performance:

Primary outcome variable of our study was clinical performance. 5 Out of 10 studies used the VAS score as outcome parameter. No evidence was found in the included studies to indicate that PEEK cages lead to significant more reduction of pain compared to other graft materials. MCID of the VAS (scale 1-10), obtained from literature, ranged between 2.5 – 2.6 for neck pain (66, 67), 2.5 – 4.6 for arm pain (66, 67), and 1.5 – 2.5 for VAS in general (43, 66). 1 out of 5 studies measured VAS scores only at follow-up (65). Therefore VAS improvement scores could not be calculated

and compared to the MCID. 3 out of 5 studies found VAS improvements scores which exceeded the MCID ranges and therefore were clinically relevant (58, 60, 61). In the last study the VAS arm improvement scores lay within the range of the MCID obtained from literature. The VAS neck improvement scores were below the threshold of the MCID and therefore were not clinically relevant (63). However, the authors estimated the MCID of both arm and neck VAS to be lower (2.0 points) compared to the values obtained from literature. According to their own interpretation of the MCID, the authors concluded the VAS arm and neck both showed clinical improvements in the majority of the population in their study (63).

Multiple other clinical outcome variables were also analyzed. However, few differences between PEEK cages and other grafts were found. PROLO scores were significantly higher in patients treated with PEEK cages compared to AICG (59). A 30% improvement from baseline was chosen as the MCID of the PROLO score, since no evidence was found in literature (43). However, because the PROLO scores were only measured during follow-up in the selected study, average improvement of the PROLO score could not be compared to the MCID.

Autograft alone leads to lower ODOM scores compared to PEEK cages, but this was also found after autograft with anterior plating (60). Because the ODOM score is used to determine the satisfaction rate after surgery, improvement scores could not be calculated. Therefore, the MCID could not be determined.

2 out of 10 studies evaluated NDI scores. Both studies found no differences between groups (Vanek et al; Cabraja et al). The MCID of the NDI, obtained from literature, ranged between 7.5 – 10.5 (66, 68). However, in one study the improvement scores for the NDI could not be calculated because the NDI was only measured during follow-up (65). Comparison with the MCID was therefore not possible in this study. NDI improvement scores in the second study exceeded the range of the MCID and therefore were clinically relevant (69).

Cervical ODI scores were evaluated in one study (61). No differences were found between groups. The MCID of the ODI could only be obtained from a lumbar study (10 points) (43). Therefore, a 30% improvement from baseline was chosen as the

MCID (43). ODI improvement scores for both groups exceeded both the 10 points and the 30% improvement rate from baseline, and therefore were clinically relevant.

JOA scores found no difference between the groups in 2 studies (58, 62). A 30% improvement from baseline was chosen as the MCID of the JOA score, since no evidence was found in literature (43). One study showed JOA improvement scores which exceeded the MCID and therefore were clinically relevant (58). The second study only measured the recovery rate at follow-up. Comparison with the MCID was therefore not possible (62)

Based on all clinical outcome scores, we can conclude there is only limited evidence that the use of PEEK cages results in better clinical improvement compared to allograft or autograft. Yu et al showed that the use of titanium cages also result in better clinical improvement scores compared to allograft or autograft (70). In our review, no differences were found in clinical outcome scores between PEEK cages and titanium cages.

As reflected in these results, a large variety of clinical outcome scores are used for the assessment of outcome after interbody fusion. Also, there is no consensus on the amount of improvement which qualifies for a clinical success. This hampers comparison between different trials. Several studies already highlighted the importance of standard clinical outcomes scores (32, 71). This review confirms this. The MCID can be a meaningful tool for comparison between different clinical outcome scores. Multiple values for several clinical outcome scores have been proposed during the last years (43, 66-68, 72, 73). Differences result from variation in population and methods used for determination of the MCID (72). Some consensus has been reached to what extends to reasonable MCID values, which we used in this review (43, 66-68, 72). We encourage future studies to include the MCID as a standard outcome clinical measure.

Radiographic scores:

Many surgeons believe that patients with radiographic fusion exhibit more clinical improvement than those who have an unsuccessful fusion. However, this remains controversial as there is no clear evidence in literature confirming this statement.

For example, Park et al found a better reduction of back pain in patients with a solid radiographic fusion 2 years after translaminar lumbar interbody fusion (TLIF) compared to those with nonunion. However, leg pain and functional outcome were similar in both groups (74). Still, a solid fusion is considered to be the primary outcome of interbody fusion. 7 out of 10 studies in our review analyzed the fusion rate of PEEK cages, which differed from 88-100%. These findings are consistent with literature describing non-comparative cohort studies (75, 76). Only 1 study found a significant higher fusion rate in favor of PEEK (14). However, different or unknown radiographic criteria are used to determine the fusion rate in each study. In literature there is no consensus on the radiographic criteria which quantify for a solid bony fusion (77-79), but a lumbar fusion study suggested that the fusion rate can be measured best with both radiogram and CT after 1 year (77). In our review 3 out of 10 studies used both radiograms and CT to determine the fusion rate. None of these studies found significantly higher fusion rates for PEEK cages. Therefore, it is difficult to draw conclusions from these results. Next to clinical outcome scores, the use of standard criteria to determine the fusion rate should be promoted, such as suggested by the criteria mentioned in the lumbar fusion study (77).

Cage subsidence is also an important factor in evaluating the outcome of fusion. It is suggested that if a cage subsides into the vertebral body, a subsequent loss of disc height , foraminal height and lordosis is to be expected, thus influencing the clinical outcome (80). Fixation by an anterior cervical plate or pedicle screws provide more stability and are therefore expected to reduce these complications (81, 82). In literature there is no consensus on the minimal loss of disc height which defines subsidence. In this review, Niu et al defined subsidence as collaps > 3 mm, which was significantly higher with the use of titanium cages compared to PEEK cages (14). Unfortunately, most articles included in this review did not define subsidence. Since there was a large variety in subsidence rate of PEEK cages reported, no conclusions can be made.

Cages allow for restoration of height of the intervertebral and foraminal space, thus relieving potential symptoms caused by compression of the exiting nerve roots. Foraminal height is described in only 2 out of 10 studies. Both studies found a significant better correction of foraminal height during follow up for PEEK cages

compared to bone grafts (58, 59). As to be expected, studies evaluating the changes in disc height confirm these results. A possible explanation can be found within the higher rate of graft collaps, as described by Cho et al (59). Unfortunately, comparisons between PEEK and titanium cages were not available.

Reconstruction of lordotic angle is important for restoring the sagittal balance of the spine. Sagittal malalignement due to local loss of lordosis could increase biomechanical stress on the anterior vertebral elements in adjacent segments, thus promoting adjacent segments disease (83, 84). It is suggested lordosis may even be more important for the long-term clinical outcome than cage subsidence (80). In this review, 6 out of 10 studies have reported on the lordotic angle. No differences were found between PEEK and titanium cages (65, 85). 50% of the studies found better correction of lordosis with PEEK cages compared to bone graft (59, 60). This can also be explained by the higher amount of bone graft collaps as described by Cho et al (59).

Biomechanical aspects:

Cages are designed to contain a bone graft, allowing bony fusion of the adjacent segments. For a durable result, this solid bony fusion is needed. Material, mechanical and biological factors of the cage play an important role in correcting spinal deformities and creating an optimal environment for spinal fusion (23, 86, 87). For example, mechanical stability is determined by the size and geometry of the cage (88, 89). Cage stiffness is an important factor in stress shielding (90, 91). Biological factors, such as the osteointegration of the cage influence quality, speed and attachment of newly formed bone (86).

In the literature, conflicting evidence is found on the biomechanical qualities of PEEK cages. A finite element study found stress magnitude in the endplate region was less for PEEK spacers as compared to titanium. As PEEK has a Young`s modulus much closer to that of cortical bone compared to titanium (E= 3.6 GPa vs. E = 110 GPa), this might lead to less subsidence and higher rates of fusion for PEEK cages (92). On the other hand, a cadaveric study found a lower primary fixation and stability of PEEK cages compared to titanium cages after anterior lumbar interbody fusion (ALIF) (93). Encapsulation of PEEK cages by a fibrous tissue layer, thus prohibiting direct cage-

to-bone contact, has been described in literature (40). The rough surface of alloyed titanium cages provides a better osteogenic environment compared to PEEK cages (94). Theoretically this should be reflected in better clinical and radiological outcome scores, but this review does not confirm this theory.

Limitations:

Best evidence was selected with the use of several quality assessment scales. A 50% threshold was chosen for inclusion, as recommended by the Cochrane Back Review Group and Newcastle-Ottawa quality scale (54). However, this cut-of point remains arbitrary. Patient selection was specified by exclusion of patients after revision surgery, spondylodiscitis, vertebral tumors, vertebral fractures or scoliosis. Only cervical fusion studies were included due to the limited number of available lumbar fusion studies. Still, different cervical fusion techniques (e.g. with or without screw or plate fixation) are described. Furthermore, indications for surgery of the included studies varied (e.g. radiculopathy, myelopathy, radiculo-myelopathy). A meta-analysis was therefore not performed due to the heterogeneity of the population of selected articles.

Suggestions

Despite the use of several quality assessment scales, no Level I evidence studies were identified. Selected RCTs and prospective studies lacked several essential (mainly statistical) prerequisites to be validated as Level I studies. To avoid possible bias in results, patients and researchers should be blinded for type of intervention during follow-up. Furthermore, radiographic assessment of fusion should be performed by radiograms and CT (77) and evaluated by independent radiologist. Also, standard clinical outcome parameters should be used as suggested by Jacobs et al and Pietrobon et al (32, 71). The MCID can be a meaningful tool for comparison between different clinical outcome scores and therefore should be included in the analyses of results in future studies. Next to this, the majority of selected studies were underpowered for detecting a clinical relevant difference. Future studies should therefore need to improve their methodology to minimize risk of bias. Unfortunately, no long-term follow-up studies could be identified in literature. To evaluate the long-term outcome of PEEK cages, publication of their results should therefore be promoted. Finally, only a few lumbar fusion studies with PEEK cages could be identified during our literature search. Therefore we decided to only include cervical

interbody studies. However, differences in clinical and/or radiographic scores are more likely to be demonstrated in the lumbar spine, as fusion rates between allograft, titanium and PEEK cages differ in this part of the spine. Publication of lumbar fusion studies could be of interest and should therefore also be promoted.

Conclusion

High fusion rates and good clinical outcome scores are reported for PEEK cages in the cervical spine. Only minimal evidence for better clinical and radiographic outcome is found for PEEK cages compared to bone grafts. No differences were found between PEEK, titanium cages and carbon fiber cages. Still, limitations are seen with PEEK cages. A lack of osteointegration of the cage and difficulty in radiographic assessment justifies the need for improvement. To improve the quality of research, standard clinical and radiographic outcome parameters should be used in future studies. Also, methodology needs to improve to minimize risk of bias. Publication of lumbar interbody fusion studies needs to be promoted since differences in clinical and/or radiographic scores are more likely to be demonstrated in this part of the spine.

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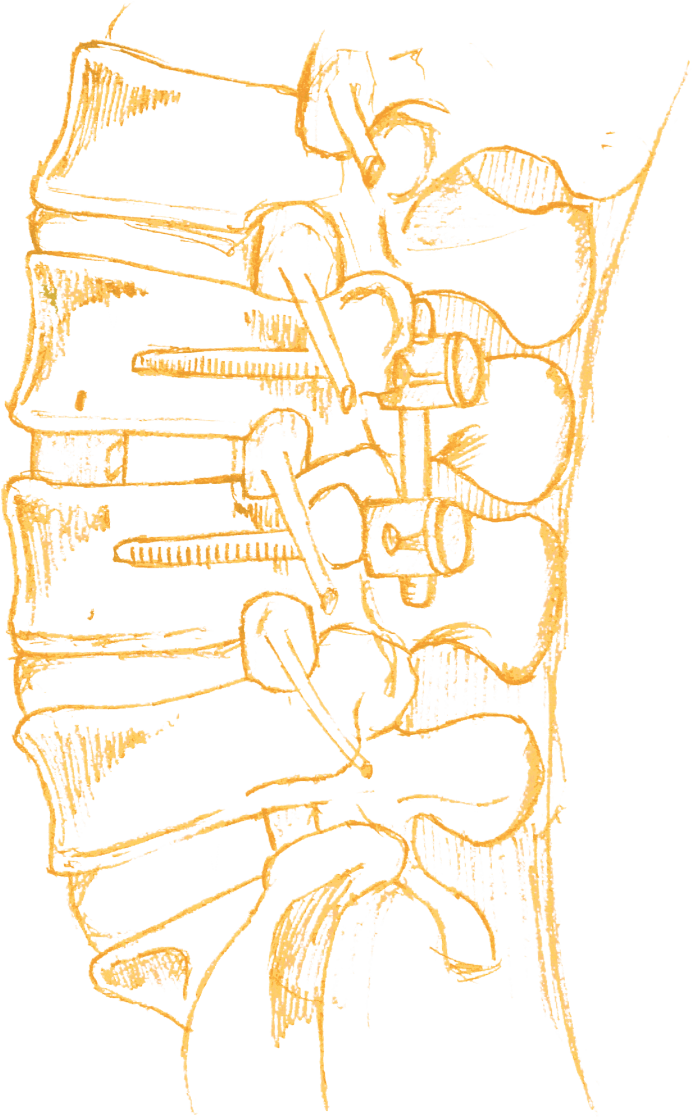
PART II.

CHALLENGES IN SURGICAL FUSION TECHNIQUES: THE SNAP TRIAL



4

COMPARISON OF PEEK VERSUS SILICON NITRIDE INTERVERTEBRAL SPACERS IN A CAPRINE MODEL

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ABSTRACT

Polyetheretherketone (PEEK) is commonly used as a spinal spacer for intervertebral fusion surgery. Unfortunately, PEEK is bioinert and does not effectively osseointegrate into living bone. In contrast, comparable spacers made of silicon nitride (Si3N4) possess a surface nanostructure and chemistry that encourage appositional bone healing. This observational study was designed to compare the outcomes of these two biomaterials when implanted as spacers in an adult caprine model. Lumbar interbody fusion surgeries were performed at two adjacent levels in eight adult goats using implants of PEEK and Si3N4. At six-months after surgery, the operative and adjacent spinal segments were extracted and measured for bone fusion, bone volume, bone-implant contact (BIC) and soft-tissue implant contact (SIC) ratios, and biodynamic stability. The null hypothesis was that no differences in these parameters would be apparent between the two groups. Fusion was observed in seven of eight implants in each group with greater bone formation in the Si3N4 group (52.6%) versus PEEK (27.9%; p=0.2). There were no significant differences in BIC ratios between PEEK and Si3N4, and the biodynamic stability of the two groups was also comparable. The results suggest that Si3N4 spacers are not inferior to PEEK and they may be more effective in promoting arthrodesis.

1 Introduction

Spinal fusion is performed to treat symptomatic degenerative intervertebral disc disease when non-operative measures are no longer effective. Of the available therapies, intervertebral fusion is generally preferred to posterolateral fusion because of higher arthrodesis rates and improved restoration of sagittal balance.[1,2] Interbody spacers are hollow-shaped implants designed to maintain spinal disc height and normal lordosis while capturing bone graft that facilitates fusion. These spacers, also known as cages, exhibit lower rates of pseudarthrosis and collapse compared to cortical bone alone.[3] Nowadays, there are a number of synthetic implant materials that are utilized as cages including monolithic PEEK, carbon-fiber reinforced PEEK, titanium (Ti), tantalum (Ta), nitinol, and silicon nitride (Si_3N_4).[4] Various combinations of these materials coupled with calcium orthophosphates or hydroxyapatites have also being introduced.[4] However, today, monolithic PEEK still holds a dominant position as the preferred implant material for spine fusion.

Biomedical PEEK was introduced in the 1990s and rapidly gained acceptance as a spinal spacer because of its lower cost, favorable modulus, and ease of use.[5] Its rise in popularity was accelerated because of subsidence concerns associated with stiffer materials. It was hypothesized that spacer materials with increased modulus might lead to stress shielding of adjacent bone thereby discouraging fusion.[6–8] However, other studies have shown that the initial and long-term mechanical stability of a spinal spacer may be more dependent upon its overall size and geometry than its elastic modulus.[9–11] In recent days, there has been a resurgence in the use of alternative materials to PEEK because it does not integrate into adjacent host bone and it is not visible on plain x-rays.[12] *In vivo*, PEEK spacers heal by the formation of a fibrous tissue layer. There is no direct appositional bone healing and this observation has been referred to as the PEEK "halo effect."[13,14] In reality, the hydrophobic nature of PEEK discourages osseointegration by inhibiting cell adhesion and protein absorption on the implant's surface.[15–17] Porous Ti surfaces may be more osteogenic than PEEK,[18] but Ti cages also have imaging modality drawbacks. Unlike PEEK, which is completely transparent to x-rays, Ti implants are opaque and also produce imaging artifacts using CT and MRI.[19] A systematic review showed no differences in fusion rates and clinical outcomes between PEEK and spine spacers made of other materials such as titanium alloys and carbon fibers.[12]

Silicon nitride (Si_3N_4) is a non-oxide ceramic with a combination of mechanical and chemical properties that make it suitable for use as a spinal interbody spacer.[20] The material can be made as a fully dense monolith or as a combination of dense and porous structures with high strength and toughness.[21,22] Spinal spacers made from Si_3N_4 have been implanted since 2008.[20,23,24] The material is partially radiolucent and because it is non-ferrous and non-electromagnetic, Si_3N_4 minimizes scatter and related artifacts on CT and MRI imaging.[19,25] Due to its unique surface chemistry, Si_3N_4 has been shown to be bacteriostatic against a variety of nosocomial microbial species;[16,17,26,27] and its physical, mechanical, chemical, and osteoconductive properties have been extensively described in the literature.[20,22,25,28–37]

In this *in vivo* observational study, the fusion rates, boney apposition, and bone volume formation between PEEK and Si_3N_4 spacers were compared using radiographic, histological, and biomechanical analyses in a caprine model. Adult goats were utilized because of similarities in the axial loads, disc geometry, and morphology between the intervertebral discs of humans and goats.[38,39] The null hypothesis for this study was that there would be no discernable differences between the two groups of implants for any of the measured parameters.

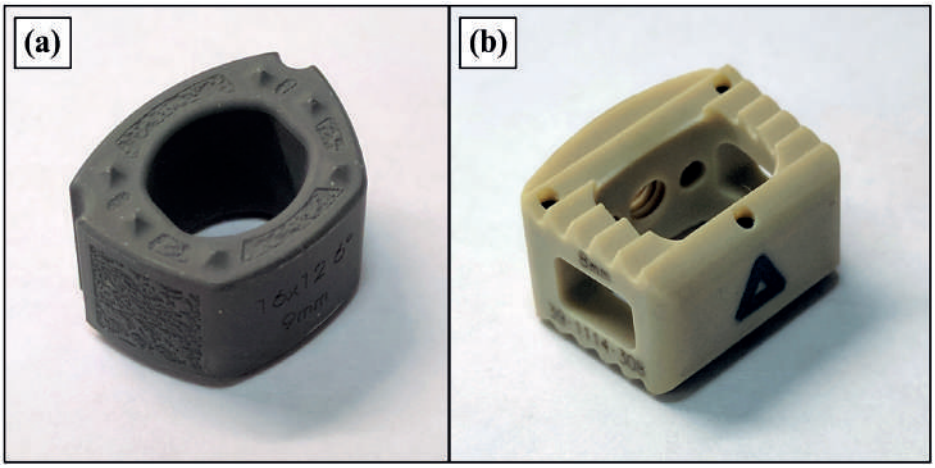
2 Materials and Methods

2.1 Implants and Implant Characterization

Since human cervical spacer sizes closely match the goat lumbar anatomy, PEEK spacers (14x11x8mm, Amedica Corporation, Salt Lake City, Utah, USA) machined from PEEK Optima® bar stock (Invibio, West Conshohocken, PA) and Valeo® Si_3N_4 spacers (16x12x8mm, Amedica Corporation) were implanted. Graft hole volumes for the PEEK and Si_3N_4 spacers were 0.46mm^2 and 0.38mm^2, respectively. The PEEK devices had a machined surface typical of polymer implants while the Si_3N_4 surfaces possessed nano-textured roughness consistent with their "as-fired" manufacturing process.[20,21] No post-densification machining was conducted on the Si_3N_4 implants. Representative photos of the Si_3N_4 and PEEK implants used in this study are provided in Figure 1(a)~(b), respectively. The surfaces of the implants were characterized for roughness, morphology, and wetting behavior using identically processed Ø12.7 x 1 mm disc

samples. Surface roughness data were acquired using white light interferometry (New-View 5000, Zygo, Middlefield, CT, USA). Data from a 0.285 mm by 0.214 mm field of view were captured using a 203 Mirau objective lens and a 2.0 multiplier. A commercially available software package (MetroPro ver. 8.1.5, Zygo, Middlefield, CT, USA) was used to calculate two roughness parameters: S_a (area average) and S_q (area root mean square).[40] Surface morphology data were obtained using a field emission gun scanning electron microscopy (FEG-SEM, Quanta, FEI, Hillsboro, OR, USA). All samples were sputter-coated with a thin »20-30 Å layer of gold (108auto, Cressington, Watford, UK) and imaged using an accelerating voltage of 10 kV at working distances of 7-10 mm and spot sizes of 4-4.5 mm. Wetting behavior was assessed using static sessile deionized water droplets having a fixed volume of 25 µL (VWR Signature Variable Volume Pipette, VWR, Radnor, PA, USA). Droplets were imaged using an optical comparator (2600 Series, S-T Industries, St. James, MN, USA) with built-in goniometer functionality. Both sides of each droplet's projected image were measured and at least eight readings per material were taken.[41]

Figure 1. Representative photographs of the implants utilized in this study: (a) Si_3N_4 and (b) PEEK



2.2 Study Design

This study was approved by the Dutch Animal Ethics Committee of the VU Medical Center. Eight skeletally-mature Dutch milk goats (60-80kg) underwent two level lumbar interbody fusions on L1-L2 and L3-L4. A PEEK spacer was implanted at one level, and a Si_3N_4 spacer at the other level. Following humane euthanasia at six

months, fused vertebrae were analyzed for biomechanical strength, and fusion quality using plain x-ray radiographs, micro-CT, and histological analyses.

2.3 Surgical Technique and Ambulatory Care

While the operative procedures utilized previously published surgical techniques,[6] a pilot examination using two animals was performed in order to make any necessary alterations and ensure safe execution of the surgical technique. In brief, after anesthesia, a 2.0 cm incision was used to access the iliac crest for cancellous bone graft, and a 20-25 cm incision in the left flank was made superficial to the transverse processes of the spine. The psoas muscle was mobilized to expose the intervertebral disc space. Under fluoroscopic guidance, the L1-L2 and L3-L4 intervertebral discs were identified with 2.0 mm K-wires placed transversely at the center of each disc space. A 6.0 mm cannulated drill was guided over the K-wire, and after removal of the K-wire, a custom block cutter was placed over the drill to make a transverse defect into the disc space and adjacent endplates. Removal of the calcified fibrocartilage from the endplates was accomplished using a sharp curette. Subsequently, each PEEK or Si_3N_4 spacer was packed with autologous iliac crest bone graft obtained from the left iliac wing and implanted in L1-L2 or L3-L4. The implantation level was chosen using block randomization for each material. Threaded Ti screws (20 x 4.0 mm, CD Horizon, Medtronic, Minneapolis, MN USA) were placed transversely into the L1 - L2 and L3 - L4 vertebral bodies, and connected with a rod for stabilization. After wound closure with absorbable sutures, all animals were rehabilitated in a facility with unrestricted outdoor and indoor access. They were monitored daily for ataxia and changes in health status over six months. After termination, the animals' lumbar spines were harvested and stripped of soft tissues with removal of screw fixation at L1-L2 and L3-L4 before further testing.

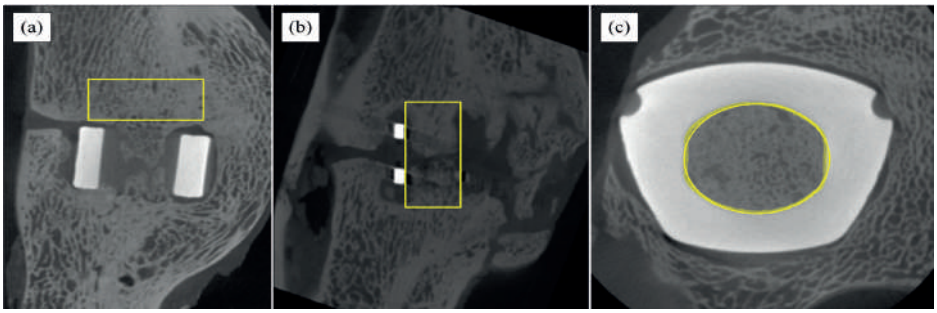
2.4 Radiographic Analyses

Standard anteroposterior and lateral x-ray radiographs were obtained pre-operatively, post-operatively, prior to euthanasia, and immediately after removing the spines. Postoperative radiographs after six months were examined for the presence or absence of a continuous bone bridge anterior to the implant. This bridge is considered a "sentinel sign" of radiographic fusion.[42] Micro-CT scans of all T13-L5 segments were made within 24 hours of harvest. The 3D spatial resolution was 80 µm

(trabecular parameters) and 42 µm (bone implant contact ratio) using a tube voltage of 90 kV, current of 180 µA, and a scan time of 2 to 3 min (Quantum FX, Perkin Elmer, USA). Micro-CT images were interpreted by two experienced independent observers. Segmental fusion was assessed from sagittal images of the operated segments. On average 280 images per segment were scored for the presence or absence of a continuous bony bridge through the hollow implant center. If bridging was present, the image was scored as being fused. Conversely, if bridging was absent, then the image was scored as not being fused. The total fusion percentage was determined by calculating the number of images demonstrating a continuous bony bridge divided by the total number of images. The volume fraction of bone (BV) and trabecular thickness were calculated using a local thresholding algorithm (Sauvola, imageJ). Since the embedded metal markers in the PEEK spacers created image distortion, measurements were limited to above the implant (region of interest (ROI-1) (12.80 x 5.2 x 12 mm)) and the middle column (ROI-2) (6.72 x 13.52 x 0.8 mm) of the spacer between the markers. Equivalent areas were also measured in the Si_3N_4 group. Bone volume/total volume ratios (BV/TV) were then determined. Bone-implant appositional contact ratios (BIC) were calculated based on high-resolution images (42 µm spatial resolution) in a 3D-voxel thick ring-shaped region of interest sandwiched between the outer and inner walls of the Si_3N_4 cages' thickness (ROI-3). Figure 2 shows the respective regions of interest. The metal markers induced image distortion for the PEEK group which precluded BIC ratio measurements both within and outside these spacers.

Therefore, BIC ratios for both groups were also estimated by histological analysis as described in the following section. However, since the histological data only represent one section of the segment, 3D model reproductions using micro-CT were also used to provide additional insight. Bernhardt *et al.* reported that 3-4 histological sections per sample are needed to sufficiently represent the BIC and BV measurements because significant intra-sample variations in BIC ratios of up to 35% were seen in studies when using only 1 or 2 sections.[43]

Figure 2. Regions of interest (ROI) used in assessing fusion: (a) ROI-1 was used to calculate the volume fraction of bone (BV) and trabecular thickness, (b) ROI-2 was used to calculate BV in the middle column of both the PEEK and Si_3N_4 cages, and (c) ROI-3 was used to calculate bone-implant contact ratios (BIC) for the Si_3N_4 cages



2.5 Histological Analysis

Spine segments were fixed in a neutrally-buffered 10% formalin solution for 4 weeks. The specimens were then dehydrated in ascending grades of ethanol and embedded in methyl-methacrylate (MMA). After polymerization, 1 mm thick mid-sagittal sections were made using a water-cooled high speed microtome with a diamond saw blade (Leica SP 1600, Leica Biosystems, Nussloch GmbH, Germany). The sections were then polished and surface-stained with McNeal's Tetrachrome, basic Fuchsine, and Toluidine Blue O, as previously reported.[44] The bone-implant (BIC) and soft tissue-implant contact (SIC) ratios were subsequently analyzed on light micrographs using 10x magnification. The area densities of bone tissue including mineralized bone, osteoids, and soft tissue were estimated using a point-counting technique.[45]

2.6 Biomechanical Analyses

All mechanical testing was performed four hours after euthanasia. Four lumbar spines (T13-L5) underwent 4-point bending tests using previously-published protocols.[46] Briefly, flexion, extension, lateral bending, and axial rotation were measured for each spine at mobile segments from L1-L4 using the intact L2-L3 segment as the control. The device was driven by a Zwick mechanical material testing system (Zwick Roell, Ulm, Germany) mounted on a hydraulic mechanical testing machine (Instron 8872, Canton MA, USA). The specimens were placed in a horizontal position. Light emitting diode (LED) markers were subsequently placed on segments L1 to L4. The T13-L1 and L4-L5 disc spaces were allowed full movement. The LED motion was captured

by an optoelectronic 3D movement registration system with an array of 3 cameras (Optotrak 3020, Northern Digital Inc, Waterloo, ON). Before testing, the Optotrak system was aligned with the anatomic axes of the spinal segment. Moments of 3.0 Nm were gradually applied in flexion/extension, right and left lateral bending, and right and left axial rotation, with a rotational speed of 1.0° per second. The maximum applied load in axial rotation was 2.0 Nm and each specimen was tested for ten continuous cycles. Mean values were compared between groups using a customized version of Matlab software for data analyses (Mathworks, Torrance, CA USA).[47]

2.7 Statistical Analysis

The sample size was set at n=8 based on previous similar studies.[48] Although this study was primarily designed for observational purposes, statistical analyses were performed using the Statistical Package for the Social Sciences software (SPSS 21.0, SPSS Inc., Chicago, Illinois, USA). The paired sample Student's *t*-test was used to detect significant differences between groups at a p value of < 0.05. Correlations were analyzed using Pearson`s rank two-tailed correlations coefficients. A coefficient of 0.5-0.75 indicated an adequate positive correlation and a > 0.75 coefficient indicated a good positive relationship. A post-ad-hoc power analysis was conducted subsequent to the experiment's completion.

Table 1. Physical and Mechanical Properties of the PEEK and Si_3N_4 Implant Materials Used in this Study.

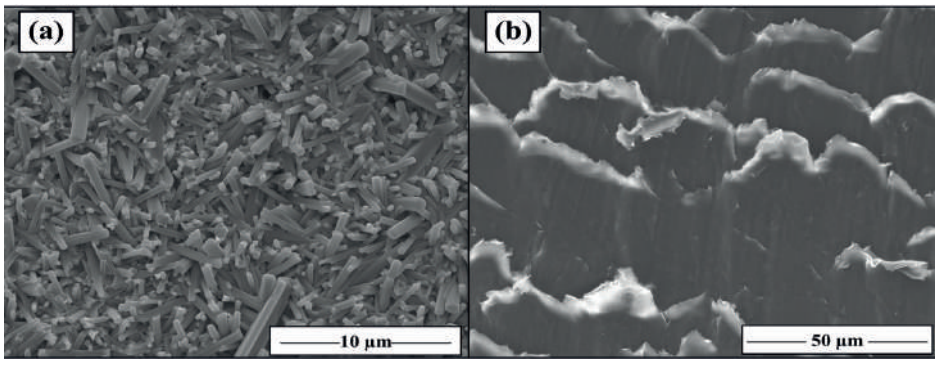
Property	Implant Material	
	PEEK	Si_3N_4
Density (g/cc)[8]	1.29	3.22 – 3.35
Flexural Strength (MPa)[8]	170	800 – 1000
Elastic Modulus (GPa)[8]	4	296 – 313
Surface Roughness (nm)		
Average, (S_a)	819	641
Root Mean Square, (S_q)	1034	830
Sessile Water Contact Angle (°)	86 ± 4	66 ± 12
X-Ray Radiolucency[8]	Transparent	Radiolucent

3 Results

3.1 Implant Characterization

The physical, mechanical, and surface morphological properties on the two implant materials are compiled in Table 1 and shown in Figures 3(a)~(b). Of note are dissimilarities in flexural strength and elastic modulus. PEEK is considered a brittle plastic of relatively low strength (170 MPa) whereas Si_3N_4, although also a brittle material, has a strength value that is »5 times that of the biopolymer (800 – 1000 MPa). With regards to elastic modulus, Si_3N_4 is a very rigid material (»300 GPa) while PEEK has a modulus that is similar to cortical and cancellous bone (»4 GPa). The surface roughness values of the two materials were similar (*i.e.*, S_a of between 641 and 819 nm; S_q of between 830 and 1034 nm). However their topographical features were considerably different. As-fired Si_3N_4 had a nano- to micro-rough surface consisting of prismatic silicon nitride grains that protrude in random directions (*cf.*, Figure 3(a)) while PEEK had a typical repetitive pattern on its surface due to machining (*cf.*, Figure 3(b)). Sessile water contact angle measurements indicated that both materials had moderate hydrophilicity (*e.g.*, defined as < 90°) with the Si_3N_4 exhibiting approximately a 20% improvement in wetting behavior in comparison to PEEK. Lastly, due principally to their differing chemical compositions, PEEK materials are radiographically transparent to X-rays whereas Si_3N_4 is partially radiolucent.

Figure 3. SEM evaluation of the surface topography of the implants used in this study: (a) Si_3N_4 and (b) PEEK.



3.2 Animal Care and Ambulation

None of the goats had existing preoperative spinal deformities per preoperative x-ray radiographs. Because of an intraoperative screw failure at L2 in one animal (*i.e.*, goat number 6, PEEK implant), spine stabilization relied on a transverse screw fixation at the L3-L4 level only. In this animal, revision surgery at one week after the index operation was attempted in order to add an additional transverse screw at level L1-L2. However, this procedure was abandoned because of a large amount of adhesions. The goat uneventfully recovered and therefore it was not excluded from subsequent analyses. In another animal, a retroperitoneal cyst was observed at the L1-L5 level during autopsy. Cultures showed no micro-organisms; consequently this animal was also included in all analyses.

3.3 Radiographic Analyses

The "sentinel sign" of fusion was present in five of eight PEEK spacers and in seven of eight Si_3N_4 spacers; whereas no "sentinel signs" were present in the control, non-operated segments as expected. Using micro-CT, seven of eight segments in both the PEEK and Si_3N_4 spacer groups showed continuous bony bridging connecting adjacent endplates through the spacers' cores. The mean percentage of micro-CT slides showing bridging through the PEEK group was 27.9% compared to 52.6% for the Si_3N_4 spacers. Figure 4(a) provides fusion percentages for each individual animal. Figure 4(b) and Table 2 present fusion averages and standard deviations for all of the spacers from both groups. Note that the difference in fusion between the two groups did not reach statistical significance (p=0.20) due to a broad variation of results within and between individual animals (*cf.*, Fig. 4(a)).

Table 2. Comparative Fusion and Bone Volume Measurements for PEEK and Si_3N_4 Implants Based on Micro-CT Image Analysis.

Measurement	Material	n	Min.	Max.	Mean ± SD	*p*-value
% Fusion	PEEK	8	0.0	79.6	27.9 ± 31.4	0.20
	Si_3N_4	8	0.0	96.5	52.6 ± 40.9	
% BV/TV Middle Implant	PEEK	8	37.6	66.3	54.7 ± 9.5	0.17
	Si_3N_4	8	32.8	84.7	65.7 ± 19.2	
% BV/TV Above Implant	PEEK	8	7.2	72.5	57.9 ± 21.1	0.69
	Si_3N_4	8	45.4	71.7	61.2 ± 9.1	

Figures 5(a)~(b) provide micro-CT images of successful fusions for spinal segments stabilized by both PEEK and Si_3N_4 spacers. Note that there was a continuous bone bridge through the graft hole of each of these implants. However, additional micro-CT analyses also indicated that there was no correlation between the fusion percentage and the presence of a continuous anterior bone bridge.

Figure 4. Assessed segmental fusion by micro-CT in: (a) Individual animals, and (b) By material type (means and standard deviations).

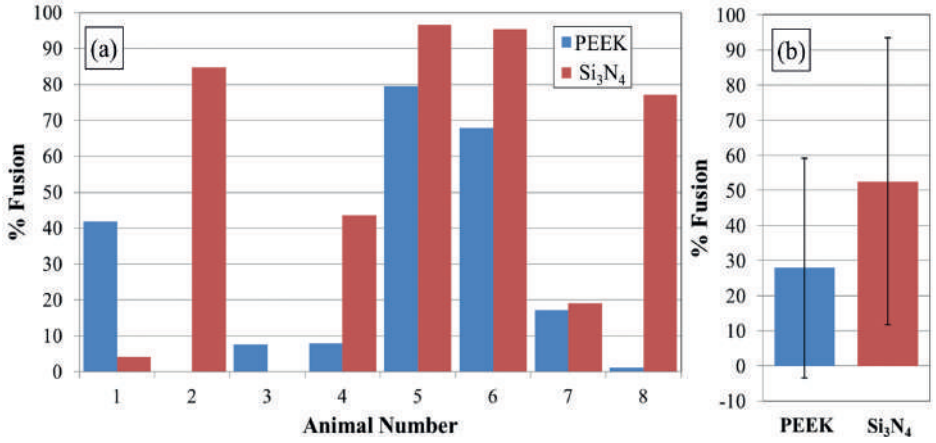
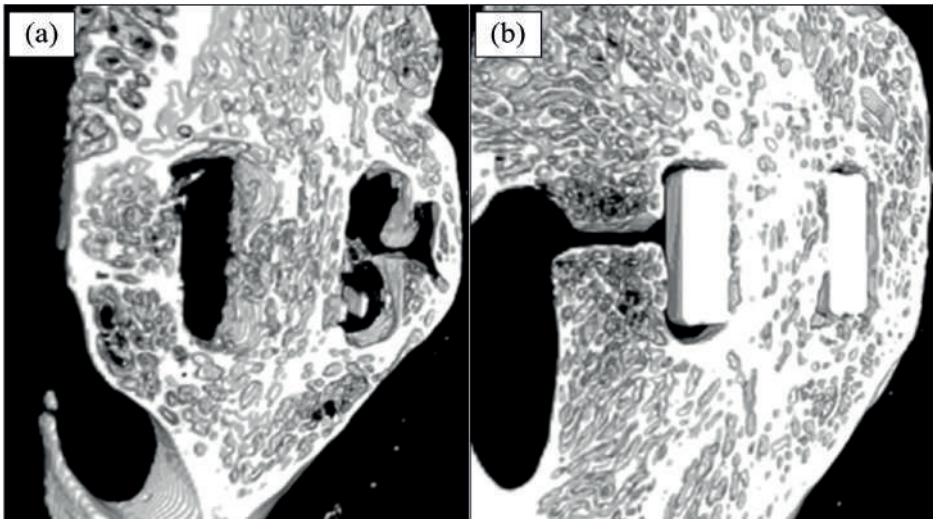
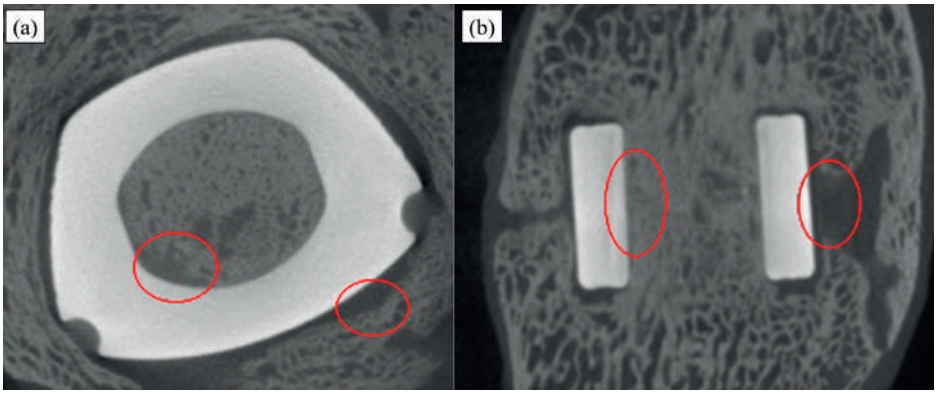


Figure 5. Micro-CT 3D reconstruction images of successful fusion showing bone growth throughout the graft hole as well as a continuous anterior bone bridge (i.e., the "sentinel sign"[41]) in: (a) a PEEK cage, and (b) a Si_3N_4 cage (2.4 mm segment).



Bone volume/total volume (BV/TV) analyses are provided in Table 2. Average BV/TV ratios for the PEEK versus the Si_3N_4 segments in the middle column were 54.7% and 65.7%, respectively (p=0.17). BV/TV ratios for bone formed above each of the implants did not substantially differ from values within the graft hole (*i.e.*, 57.9% and 61.2% for the PEEK and Si_3N_4 groups, respectively *cf.*, Table 2). Fusion percentages correlated positively with higher BV/TV values (r=0.66, p=0.01). As mentioned previously, the metal marker-induced image distortion within the PEEK group precluded BIC ratio measurements both within and outside these spacers. However, BIC ratios were independently calculated for the Si_3N_4 implants. It was observed that the BIC ratio outside of the Si_3N_4 implants was slightly lower than the inside (7.5±9.9% versus 9.0±7.8%, n = 8 each, respectively) although this difference was not significant. There were no correlations between the percentage of fused segments and BIC ratios inside or outside of the Si_3N_4 cages. Figure 6 illustrates a Si_3N_4 implant with differences in BIC on the inside and outside of the cage on a transverse and sagittal view.

Figure 6. Micro-CT images of Si_3N_4 implant showing differences in the appositional bone-implant contact ratio (BIC) inside and outside of the implants on (a) a transverse view, and (b) a sagital view.



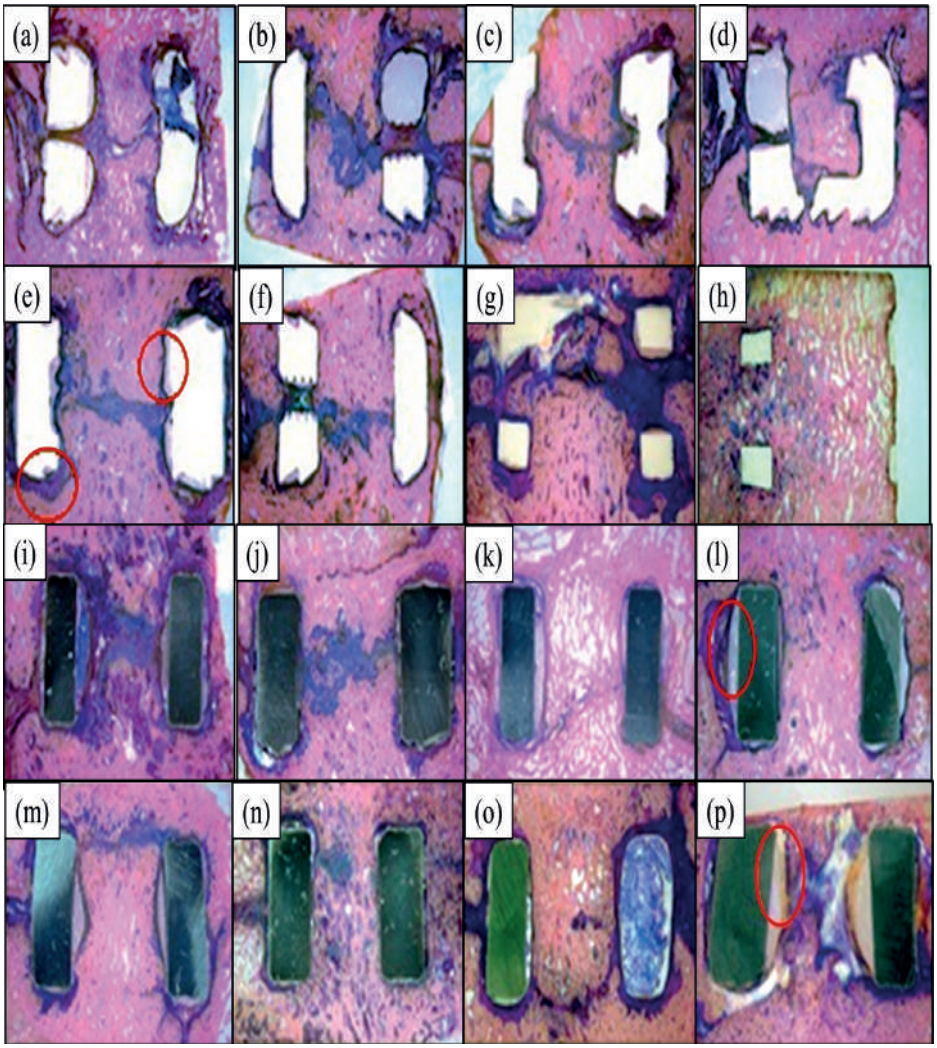
3.4 Histological Analysis

Figure 7(a)~(h) and (i)~(p) show histological section views of the PEEK and Si_3N_4 implants, respectively. Bridging bone was more consistently observed with the Si_3N_4 implants. Areal measurements of total bone tissue (*i.e.*, collagen and hydroxyapatite) for the PEEK and Si_3N_4 groups was assessed to be 75.1% versus 74.8%, respectively; whereas actual mineralized bone was determined to be 56.3% versus 54.9%, respectively. The differences in these two sets of data were not significant. Calculated values for appositional tissues are provided in Table 3. In spite of the presence of strong bone growth throughout each of implant groups, appositional soft tissue dominated the implant's interfaces. The SIC ratios for the PEEK and Si_3N_4 groups were 93.2% and 89.2% for inside of the implants, and 94.4% and 97.8% for outside of the implants, respectively (*cf.*, Table 3). No statistically relevant differences were noted for these results as well.

Table 3. Histological Analysis of Appositional Bone and Soft Tissues in the PEEK and Si_3N_4 Implant Groups.

Measurement	Material	n	Min.	Max.	Mean ± SD	*p*-value
% BIC Inside	PEEK	8	0.0	33.3	6.8 ± 12.2	0.63
	Si_3N_4	8	0.0	43.5	10.8 ± 18.9	
% SIC Inside	PEEK	8	66.7	100.0	93.2 ± 12.2	0.63
	Si_3N_4	8	56.5	100.0	89.2 ± 18.9	
% BIC Outside	PEEK	8	0.0	41.9	5.6 ± 14.7	0.55
	Si_3N_4	8	0.0	12.5	2.2 ± 4.6	
% SIC Outside	PEEK	8	58.1	100.0	94.4 ± 14.7	0.55
	Si_3N_4	8	87.5	100.0	97.8 ± 4.6	

Figure 7. Histological sagittal sections of the inside and outside of all extracted spacers for assessment of appositional bone-contact (BIC) and soft-tissue contact (SIC) ratios for: (a-h) PEEK implants, and (i-p) Si_3N_4 implants. The pink color corresponds to bone; the blue and white colors correspond to soft tissues. Note that a significant amount of appositional soft-tissue was observed for most of the implants (cf., Table I). This is particular present for the PEEK component shown by the circular inset in (e) and the Si_3N_4 implant in (l) and (p).



3.5 Biomechanical Analysis

Results are provided in Table 4. As expected, significant differences in the ranges of motion (ROM) were detected between fused and non-fused control spine segments regardless of the spacer material with *p*-values as low as 0.003 (*cf.*, Table 4). Good correlation coefficients were observed between flexion/extension and lateral bending (r=0.71), between flexion/extension and axial rotation (r = 0.74), and between lateral bending and axial torsion (r=0.78). These results are consistent with other similar studies.[46] However, no differences in ROM were detected between segments fused with either PEEK or Si_3N_4 (*i.e.*, *p*-values ranging from 0.74 to 1.00). In fact, both implant groups appeared equally effective in achieving fusion for their respective segments based on these observations. Also, there were no significant correlations between the biomechanical results and the imaging assessments of fusion for either of the materials or any of the operative segments.

Table 4. Biomechanical Analysis – Range of Motion (°) for Control (Non-Operative), PEEK (Operative), and Si_3N_4 (Operative) Groups.

Measurement	Material	n	Min.	Max.	Mean ± SD	*p*-values*
Flexion/Extension	Control	4	7.46	8.54	7.87 ± 0.51	$p_1 = 0.05$
	PEEK	4	0.44	7.46	2.61 ± 3.26	$p_2 = 0.06$
	Si_3N_4	4	1.00	6.94	3.38 ± 2.88	$p_3 = 0.74$
Lateral Bending	Control	4	6.63	15.62	10.64 ± 4.38	$p_1 = 0.03$
	PEEK	4	0.82	5.32	2.24 ± 2.09	$p_2 = 0.04$
	Si_3N_4	4	1.08	4.02	2.34 ± 1.24	$p_3 = 0.94$
Axial Rotation	Control	4	0.82	1.15	1.05 ± 0.16	$p_1 = 0.003$
	PEEK	4	0.17	0.56	0.40 ± 0.17	$p_2 = 0.07$
	Si_3N_4	4	0.14	1.06	0.40 ± 0.45	$p_3 = 1.00$

* p_1 = Difference between Control and PEEK groups; p_2 = Difference between Control and Si_3N_4 groups; p_3 = Difference between PEEK and Si_3N_4 groups.

4 Discussion

This study compared fusion rates and osseointegration of PEEK versus Si_3N_4 spacers in a caprine model because of similar axial loads, disc geometries, and morphologies of human and goat intervertebral discs.[38,39] Three accepted methods for assessing fusion differences

between these two implant groups were utilized: radiographic imaging (both x-ray and micro-CT), histological analyses, and biomechanical testing. The results indicated that both implant materials were effective in achieving fusion. The operated segments containing either the PEEK or the Si_3N_4 spacers showed significant range-of-motion restrictions on flexion/extension, lateral bending, and axial rotation in comparison to non-operated segments (*cf.*, Table 4). Bone bridging through the graft hole was apparent for the majority of implants from both groups, as was a significant amount of bone volume above each of the spacers (*cf.*, Table 2). Although fusion and bone volumes of the PEEK and Si_3N_4 groups were not statistical different (*i.e.*, $p \geq 0.05$), overall the Si_3N_4 spacers showed higher average fusion percentages and greater bone volumes than the PEEK components. The histology data correlated with the imaging analyses but also showed that soft tissue (*i.e.*, fibrous layers) dominated the interfaces between the implants and new bone growth regardless of the implant type (*cf.*, Table 3). These results were consistent with earlier findings in a similar goat model,[46] thereby confirming the validity of the current measurements.

Bone bridging between the two endplates is generally seen as an important technical determinant for successful fusion surgery.[49] However, a technically successful fusion does not necessarily equate to the same clinical outcome because vertebral stability may occur before it is radiographically evident.[42,46] While there is no consensus on the proper radiographic assessment of fusion within the clinical literature,[12] anterior bone bridging (*i.e.*, the "sentinel sign") has historically been the classic indicator of solid bony fusion using plain radiographs.[42,46] Based on criteria provided by Burkus *et al.*,[50] fusion in this study was assessed via multiple imaging techniques including plain radiographs and micro-CT. Using the "sentinel sign" as the classical definition of fusion, 62.5% of the PEEK and 87.5% of the Si_3N_4 segments were assessed as having been fused. This contrasts with the micro-CT analyses which showed fusion in 87.5% of the PEEK and Si_3N_4 implants. In fact, the micro-CT analyses showed 0% bony fusion between endplates in one PEEK and one Si_3N_4 cage whereas "sentinel signs" were present on the radiographs for both of these spacers. Figure 8 presents a micro-CT and x-ray radiographic example of this observation for a Si_3N_4 cage. The x-ray radiograph indicates the formation of an anterior bone bridge while the micro-CT shows no bone connectivity whatsoever between the two endplates. It can therefore be concluded that the presence of a "sentinel sign" on a plain radiograph is not a valid determinant or assessment of fusion. Furthermore, there was a broad range of fusion percentages observed for the cages used in this study. Since the biodynamic analyses

showed no differences in samples with either high or low segmental fusion percentages, it is difficult to suggest the amount of segmental fusion required for clinical ankylosis of the operative segment. While 7 out of 8 spacers (87.5%) from both materials exhibited a bony bridge through the graft hole, apparently the presence of even a limited amount of bone growth between the endplates still results in a mechanically stable situation.[46]

Next to mechanical, biological, and material factors, other determinants may have influenced bony fusion including endplate preparation,[51,52] implant/endplate proximity,[9,53] and implant surface topography.[4,53–55] Each of these issues could have led to micromotion and the corresponding formation of fibrous tissue around the implants. While a certain amount of movement beneficially aids fusion via the creation of mechanical strain which enhances osteoblastic activity,[9] displacements above about 40~50 μm favor fibrous tissue rather than bone.[4,56] In fact, increased amounts of fibrous tissue next to implants, radiolucencies at the implant interfaces, and the presence of subchondral cysts have been reported as clear evidence for micromotion.[50] The first two conditions were observed within the current study.

With respect to endplate preparation, best efforts were employed to remove the avascular calcified fibrocartilage layer in order to ensure a flattened surface of bleeding bone prior to insertion of the implants. Endplate preparation for each operative segment was subsequently scored by direct post-operative imaging. The sixteen segments were classified into four categories: (i) no apparent endplate preparation (n=0); (ii) intact superior endplate (n=1); (iii) intact inferior endplate (n=3); and (iv) adequate endplate preparation (n=12). A post-study analysis correlated endplate preparation to the micro-CT fusion data and the results showed no association (*i.e.*, a coefficient of -0.13, p=0.62). Inadequate endplate preparation was also discounted given the nearly equivalent fusion rates and BIC ratios for cages from both groups.

Regarding the proximity of the spacers to the endplates, the PEEK and Si_3N_4 cages were selected to be dimensionally as close as possible (*cf.*, Figure 1). Titanium rod stabilization with screw fixation was employed in an effort to minimize endplate/implant proximity effects. No radiographic differences in implant positions or migration were noted within or between animals and no subsidence was observed for any of the implants. Of note, the segment without the additional transverse screw

(goat number 6, PEEK implant) showed adequate fusion (68%) in spite of a lack of appropriate augmented fixation. Also, it is believed that the observed retroperitoneal cyst at L1 to L5 found upon the autopsy of animal number 5 was not associated with micromotion. While the etiology of this large cyst remains unknown, it was not located within the vertebrae or adjacent to the implants (*i.e.*, between the implants and endplates) which is typical for a cyst formed by micromotion. Indeed, this animal had among the highest fusion percentages within the study (*i.e.*, PEEK at 79.6% and Si_3N_4 at 96.5%). Prior research suggests that if the positioning of the implant or its relative movement are greater than 40-150 μm, then fibrous tissue integration is the likely outcome.[4] This amount of movement would have been undetectable using the imaging modalities of this study. However, although micromotion may have played a role in the increased amount of soft-tissue formation next to each of the implants (*cf.*, Table 3), there was no correlation between BIC or SIC ratios and fusion percentages.

Implant surface topography may have also played a role in the large variability observed in fusion and in the significant amount of fibrous tissue formed around both types of cages (*cf.*, Figures 6~7 and Table 3). Recent studies on a number of different materials have increasingly shown that the combination of macro- (S_a or $R_a \geq 1.0$ μm), micro- ($0.1\ \mu m \leq S_a$ or $R_a < 1.0$ μm), and nano-rough surfaces (S_a or $R_a < 0.1$ μm) are more effective in facilitating bone apposition than smooth implants.[53,54,57–60] In this study, the average area surface roughness of both cage materials was essentially equivalent (0.6~0.8 μm, *cf.*, Table 1). While the PEEK implants had some micro-rough features and the Si_3N_4 had nano-rough characteristics, neither implant had a broad topographical range in roughness values. Consequently, it is perhaps not unexpected that they had similar fusion and appositional bone healing characteristics (*cf.*, Tables 2~3). It is generally known that smooth PEEK consistently results in fibrous tissue encapsulation;[12,14,57,59–62] but there are few studies of soft-tissue formation around Si_3N_4 implants. For both materials, available data suggest that surface topography may be a contributing factor in their high SIC ratios.

For instance, in a six-month goat study comparing smooth PEEK to porous tantalum implants, Sinclair *et al*. reported that soft fibrous tissues dominated the implant interfaces: ~99% for PEEK and 87% for tantalum.[62] Although the authors failed to provide detailed topographical data on the two implants, they attributed the

appositional differences to the porous nature of the tantalum. Nevertheless, their reported soft-tissue values for PEEK are similar to those observed in the current study. In a more recent report, Torstrick *et al.* compared the osseointegration characteristics of PEEK implants having either a smooth or a 3D macro-porous surface. The porous surface was engineered to mimic trabecular bone. They monitored bone ingrowth and expulsion forces on implants in several murine models.[60] Histological analyses showed less fibrous tissue for the porous PEEK along with >40% mineralized bone in its pore spaces and twice the integration strength of the smooth PEEK. Also, Pelletier *et al*. performed a comprehensive six-month osseointegration study in an ovine model comparing smooth PEEK to titanium implants which possessed both polished and plasma-sprayed surfaces.[63] They systematically found that plasma-treated titanium surfaces had the greatest appositional bone contact (42%) followed by smooth PEEK (12%). Remarkably, the polished titanium surfaces had little direct bone contact (~6%). The PEEK and polished titanium surfaces were dominated by fibrous tissue. This work followed an even earlier study by Walsh *et al.* which provided similar results when comparing smooth PEEK to plasma-sprayed titanium coated PEEK.[57]

For Si_3N_4, Howlett *et al*. performed an implantation study using 70% porous silicon nitride plugs inserted in the femoral marrow cavities of New Zealand White rabbits for up to five years.[30] They examined two ranges of pore sizes: 255 ± 64 μm and 170 ± 45 μm. For the larger size range, they reported that at least 75% of all pores were occupied by mature lamella bone after 12-weeks *in vivo*. In contrast, the smaller size range had approximately one-third of their pores filled with osteoids at about the same time. Light-microscopy examination of long-term implants showed that the bone present inside the pores was morphologically normal; but a 5 to 10 μm layer of fibrous tissue was often found in direct contact with the implant. Later, Guedes e Silva *et al.* performed an eight-week implantation study in the tibia of New Zealand White rabbits. While they did not characterize the surface morphology of their dense Si_3N_4 implants, they qualitatively showed via histology that osteoblasts and osteocytes were in direct contact with the Si_3N_4 implants along with a matrix of collagen I and III tissues. They also found that the bone remodeling process around the Si_3N_4 implants was more pronounced than for commercially pure titanium controls.[64] Subsequently, Anderson and Olsen completed a 12 and 24-week osteoconductivity study on 72% porous Si_3N_4 plugs (450 μm average pore size) implanted in sheep femoral condyles.[65] At the two endpoints, they found one implant out of five to

be encapsulated in fibrous tissue while the remaining four had ~78% direct bone contact. Furthermore, they indicated that the amount of bone ingrowth (8.5% to 9.6%) was similar to a previous study conducted using porous titanium.[66] Histological analyses indicated that the entire 11 mm width of the porous Si_3N_4 implants had vascularized tissues comprised primarily of lamella bone and various forms of collagen, all of which were in direct contact with the implant. Lastly, Pezzotti *et al.* examined two intervertebral spinal spacers – one made from dense Si_3N_4 and the other from monolithic PEEK – that were retrieved from human patients after 11 and 14 months *in vivo*, respectively.[67] Using quantitative histology, they found that the BIC ratios inside the graft holes of the two materials were ~19% and ~0.4%, respectively. Of note, the surface morphology of these implants was identical to the ones used in the current study.

The review of these prior reports suggests that the topographical features of abiotic materials may be at least as important as their surface chemistry. The data suggest that devices with smoother surfaces are more likely to engender the formation of fibrous tissues than those with a range of macro-rough and micro-fine textures. Therefore, the data from the current study indicates that the comparable appositional healing observed by both implant materials was likely influenced more by the similarity of their surface topography than their differing chemistry. Nevertheless, the results demonstrate good osseointegration of the Si_3N_4 implants in this animal model.

Obviously, the large variability in observed segmental fusion within and between animals represents a major limitation of the current study. In retrospect, the *n* value of eight implants bilaterally placed in an equal number of animals was insufficient in assessing statistical differences between the two groups given the large observed standard deviations. A post-ad-hoc power analysis suggested that a sample size of n=25 would have been necessary to achieve at least 80% power to discern differences between the two groups using a mean difference of 24.7% and a standard deviation of 41.2%. This analysis suggests that the lack of definitive statistical significance was likely due to a type 2 error, or failure to reject the null hypothesis. Consequently, it is concluded that Si_3N_4 cages are not inferior to PEEK. In fact, they may be more effective in facilitating arthrodesis based on the observed average fusion data. Another limitation of this study is the one end-point at 6 months (~26 weeks). Other studies have shown that earlier time points may be more effective in highlighting material differences.[62]

5 Conclusions

Si_3N_4 cages had favorable radiographic imaging characteristics and showed higher fusion rates using radiographic, histological, and biomechanical analyses at 6 months after lumbar interbody fusion in a goat model compared to PEEK cages, although the results did not reach statistical significance in this observational study. Nevertheless, the data suggest that the Si_3N_4 spacers were not inferior to PEEK. In fact, they may be more effective in facilitating early adequate arthrodesis. Additional animal studies with larger *n* values are required to statistically validate this observation. However, the current findings may help to optimize future animal study designs and outcome measurements. In particular, it is recommended that detailed analyses of both the surface topography as well as surface chemistry of all abiotic implants be included in all future designs. Results from this study also provide insight into the various imaging modalities that can be utilized to assess spinal fusion. It was found that the classic use of lateral x-ray radiography to assess fusion (*i.e.*, the "sentinel sign") overestimated the actual amount of bone bridging between the endplates in comparison to micro-CT. Furthermore, the biomechanical analysis demonstrated that adequate vertebral stability can be achieved without necessarily having contiguous bone between the endplates. These findings should provide guidance to clinicians in assessing spinal fusion in human studies.

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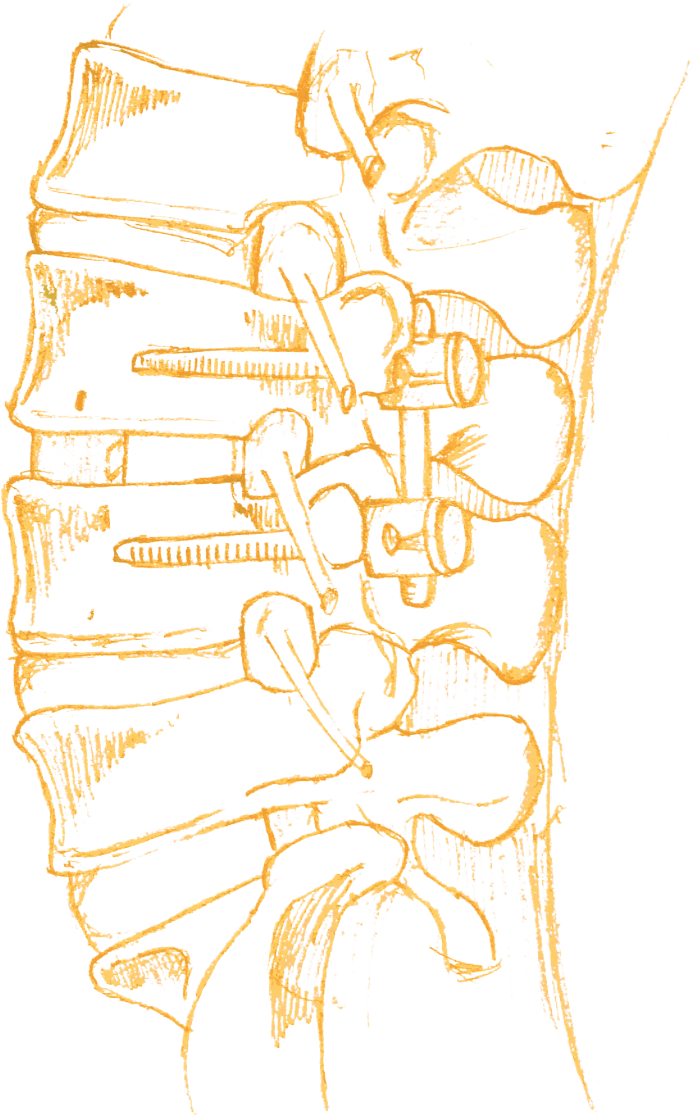

5

THE SNAP TRIAL: A DOUBLE-BLIND MULTI-CENTER RANDOMIZED CONTROLLED TRIAL OF A SILICON NITRIDE VERSUS A PEEK CAGE IN TRANSFORAMINAL LUMBAR INTERBODY FUSION IN PATIENTS WITH SYMPTOMATIC DEGENERATIVE LUMBAR DISC DISORDERS: STUDY PROTOCOL

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ABSTRACT

Background: Polyetheretherketone (PEEK) cages have been widely used in the treatment of lumbar degenerative disc disorders, and show good clinical results. Still, complications such as subsidence and migration of the cage are frequently seen. A lack of osteointegration and fibrous tissues surrounding PEEK cages are held responsible. Ceramic implants made of silicon nitride show better biocompatible and osteoconductive qualities, and therefore are expected to lower complication rates and allow for better fusion.

Purpose: to show that fusion with the silicon nitride cage produces non-inferior results in outcome of the Roland Morris Disability Questionnaire at all follow-up time points as compared to the same procedure with PEEK cages.

Study design: A double blind multi-center randomized controlled trial with repeated measures analysis.

Materials and Methods: 100 patients (18-75 years) presenting with symptomatic lumbar degenerative disorders unresponsive to at least 6 months of conservative treatment are included. Patients will be randomly assigned to a PEEK cage or a silicon nitride cage, and will undergo a transforaminal lumbar interbody fusion with pedicle screw fixation. Primary outcome measure is the functional improvement measured by the Roland Morris Disability Questionnaire. Secondary outcome parameters are the VAS leg, VAS back, SF-36, Likert scale, neurological outcome and radiographic assessment of fusion. After 1 year the fusion rate will be measured by radiograms and CT. Follow-up will be continued for 2 years. Patients and clinical observers who will perform the follow-up visits will be blinded for type of cage used during follow-up. Analyses of radiograms and CT will be performed independently by two experienced radiologists.

Discussion: In this study a PEEK cage will be compared with a silicon nitride cage in the treatment of symptomatic degenerative lumbar disc disorders. To our knowledge, this is the first randomized controlled trial in which the silicon nitride cage is compared with the PEEK cage in patients with symptomatic degenerative lumbar disc disorders.

Background

Chronic low back pain is an important reason for patients to visit general practitioners. In Europe, estimates of lifetime prevalence of chronic low back pain range from approximately 60 – 90 % (1). It is one of the leading causes of activity limitation in adults and results in high socio-economic costs and loss of quality of life (2). The exact cause of chronic low back pain is often unknown, but degenerative disorders of the intervertebral disc are held responsible (3). The pain can be eliminated by stabilizing the degenerative segment, for example as seen in the successful treatment of degenerative joints with an arthrodesis (4, 5). Spinal fusion is commonly used for stabilizing degenerative and isthmic spondylolisthesis and severe, painful disc degeneration.

In a spinal fusion, two or more vertebrae are fused after a bone bridge is created between the vertebrae, either posterior, interbody or both. Originally, bone grafts were used to promote interbody fusion. However, several complications were associated with the use of grafts. These include donor site morbidity, a decrease in the intervertebral disc space height due to graft collapse, graft subsidence, graft retropulsion, graft resorption, fusion failure with subsequent pseudarthrosis and prolonged healing time (6, 7).

As an alternative for bone grafts, interbody cages were developed (7). They are designed to be filled with bone, allowing bony fusion through the cage to the adjacent vertebrae. Both material and design of the cage play an important role in correcting spinal deformities and creating an optimal environment for spinal fusion (8-10). The development of a solid bony fusion is influenced by mechanical and biological factors. For example, the size and geometry of the cage determines the initial mechanical stability (11, 12). Furthermore cage stiffness is an important factor in stress shielding (13, 14). Biological factors, such as the osteointegration of the surface of the cage, influence quality, speed and attachment of newly formed bone (8).

Cages allow for direct axial load bearing and restore of height of the intervertebral and foraminal space. Initially, interbody cages were implanted in pairs via the traditional posterior lumbar interbody fusion (PLIF) technique. More recently, a larger single oblique cage is used that provides more stability (15, 16).

Polyetheretherketone (PEEK) materials were used in aerospace and aviation industries before researchers began exploring them in medical devices, mainly in trauma and femoral components of hip prosthesis (17, 18). Besides being radiolucent, PEEK is relatively inert and does not provoke a strong foreign body reaction in vivo (19). During the late 1990`s the first PEEK cages for spinal fusion became available. High fusion rates and good to excellent clinical outcomes have been reported compared to titanium cages and bone grafts (20, 21). Most spine surgeons therefore prefer PEEK cages over other cages.

To allow some visualization on radiograms and CT, radio-opaque markers are present in PEEK cages. The major advantage of PEEK cages over the metal cages is that they produce less artifacts on CT or MR scans. However, a radiolucent cage could also contribute to the difficulty of radiographic assessment of its exact position in the spine. For example, placement of the cage during surgery is less accurate, and follow-up imaging is more difficult. This is important to determine the cause of ongoing symptoms and/or to determine if fusion has occurred. Additional problems observed include a 14.3% rate of subsidence in patients with PEEK cages after lumbar interbody fusion (22). Furthermore, posterior migration of a component of a PEEK cage has been reported (23). It has also been reported that PEEK cages are generally encapsulated by a thin fibrous tissue layer rather than bone growing in intimate contact with the polymer (24).

Better osteointegration of the cage is believed to minimize the rate of subsidence and migration. Therefore, researchers have been working on materials that mimic the mineral content of bone for many years (25). Ceramic implants can be manufactured with a rough surface and have the potential to show a better integration with the host bone, which facilitates the attachment of bone to the implant rather than the fibrous encapsulation (24). Ceramics are strong and light-weight and have desirable imaging properties, free from artifacts on CT and MRI (26).

Silicon nitride (Si_3N_4) is a ceramic with a compression strength exceeding the usual plastic and metal materials used for interbody cages. Unlike many other ceramics, silicon nitride resists brittle fractures; its toughness exceeds that of alumina, a material with 30+ years of use in joint replacements (27). Silicon nitride is also highly compatible with standard imaging techniques. The material is free from artifacts on radiogram, CT and MRI images (26). Several studies have demonstrated its biocompatibility and

its mechanical and osteoconductive qualities in vitro (28-32). Furthermore, compared to PEEK and titanium, silicon nitride has a decreased bacterial activity on its surface (33, 34). Based on good results in vitro, silicon nitride is used in the development of bearings that can improve wear and longevity of knee and hip prosthesis (32).

A preliminary study with silicon nitride interbody cages showed good clinical and radiological results in 2 patients 1 year after a transforaminal lumbar interbody fusion procedure (35). Sorrell et al presented the results of a 10 year clinical follow-up study (36). In this study 30 patients underwent anterior interbody fusion of the lumbar spine using silicon nitride cages. They found a durable interbody fusion after 5 years (21 out of 22 patients) and after 10 years (16 out of 16 patients). Please note there was a 47% loss of follow-up. Silicon nitride materials received the CE Mark and FDA market clearance for its use as interbody cages in 2008. They have been used in the US for over 3 years, with no adverse events reported (32).

Compared to PEEK cages silicon nitride cages are expected to have lower complications rates and allow higher fusion rates due to better biocompatible and osteoconductive qualities. The purpose of this study is to compare the clinical outcomes and fusion rates of PEEK cages with silicon nitride cages in patients with symptomatic degenerative lumbar disc disorders.

Methods and design

In our study, PEEK and silicon nitride interbody cages will be compared in the treatment of degenerative lumbar disc disorders. This non-inferiority study is designed as a multi-center (two center) clinical observer and patient blind randomized controlled trial with 2 parallel treatment groups. The multi-center design is needed in order to collect enough patients for reasons of statistical power. To minimize observer bias, both patients and clinical observers will be blinded for treatment during follow-up. Clinical observers will not analyze radiograms and CT because the silicon nitride cages are clearly visible. The follow-up is 2 years, in which patients will fill out several questionnaires and are examined both clinically and radiologically.

Patient selection

Participation in our study will be requested from patients (18-75 years old) who visit the outpatient clinic in one of the participating hospitals. Patients must present with a history of chronic low back pain with or without leg pain that did not respond to conservative treatment and disc degeneration of Pfirrmann Grade III (37) or higher and/or isthmic or degenerative spondylolisthesis of Grade I or II, confirmed by MRI.

The treating physician will discuss this study with the patient and if the patient fulfills all inclusion criteria (table 1), the information form and informed consent form is handed out to the patient. The patient can read subsequently at leisure at home.

Patients who decide to participate in our study are scheduled for an appointment with the researcher at the outpatient clinic of the hospital. During this visit, the patient is extensively informed about the backgrounds, the objectives, the investigational design and the assessments of the investigation and the possible advantages and disadvantages of the investigation. All this information provided by the researcher matches the earlier provided patient information form. The patient is requested to sign the informed consent. Pre-operative baseline data will then be collected for the outcome scores as well as patient's demography. A neurological examination is performed, the MRI and other tests are reviewed and the surgery is discussed. All patients preoperatively visit an anesthesiologist for standard medical assessment. All patients will be operated under general anesthesia.

Randomization

Patients who meet the inclusion and exclusion criteria, and have given informed consent are allocated the next available investigational number (Patient ID number) and will be randomly allocated to one of two groups (treatment A or treatment B) by use of a centralized 24-hour computerized randomization system that allows internet randomization (Sealed Envelope Ltd. London). After completing follow-up at 2 years post-surgery both patient and researcher will be informed which cage was used.

Table 1: inclusion and exclusion criteria

Inclusion criteria	- Male and female patients age 18-75 years - Chronic low back pain unresponsive to at least six months of conservative care - MRI and standing x-ray evidence of Pfirrmann Grade III or greater disc degeneration and/or degenerative or isthmic spondylolisthesis of Grade I or II - Signed informed consent
Exclusion criteria	- Osteoporosis - Patients with prior failed fusion at the same level - Degenerative scoliosis - Degenerative spondylolisthesis greater than Grade II - Pregnancy - Psychiatric or mental disease - Alcoholism (drinking more than 5 units per day) - Active infection or prior infection at the surgical site - Active cancer - Insufficient language skills to complete questionnaires - Participation in another study - More than two symptomatic levels that need fusion - Planned (e)migration abroad in the year after inclusion

Surgical Management

Patients will undergo a transforaminal lumbar interbody fusion with an oblique single PEEK or SiN cage (Amedica Corporation, Salt lake City, Utah) supplemented by pedicle screw fixation, as described by Harms et al (38). Design of the PEEK cage is similar to the SiN cage. Autograft bone extracted from locally excised bone from the lumbar spine will be used for cage filling. After surgery, patients will be admitted for 3-4 days. Patients are encouraged to mobilize as soon as possible. A lumbar support orthosis is not prescribed.

Outcome measurements

Several validated questionnaires described below will be used for outcome assessments. During intake, a basic physical exam with neurological examination (muscle strength, reflexes) and additional assessments as required per normal practice will be performed to ensure that the patient can undergo surgery safely. During follow-up visits at 3, 6, 12 and 24 months the neurological examination will be repeated. See table 2 for the patient follow-up chart.

Table 2: Follow-up chart

	Intake	Admission	3 months	6 months	12 months	24 months
Visit	1	2	3	4	5	6
Demography	X					
Study information + informed consent	X					
Randomization	X					
Surgery		X				
Operative data		X				
Neurological examination	X		X	X	X	X
Questionairres: - Roland Morris Disability Questionairre - SF-36 - VAS back - VAS leg - Working status	X		X	X	X	X
Likert scale		X	X	X	X	X
X-rays	X	X	X	X	X	X
CT					X	
MRI	X					
Complications		X	X	X	X	X

Primary outcome measure

Primary outcome will be measured by the Roland Morris Disability Questionnaire (RMDQ). The 24 point RMDQ is a widely used patient-completed measure of health outcome for low back pain (39-41). The patient will complete the Dutch version of the questionnaire, which is validated for the Dutch population (42), and the sum of the scores will be used to measure disability. The score ranges from 0 to 24, with a higher score indicating more severe disability. Primary objective is to measure the average improvement in RMDQ for the silicon nitride patients versus those that receive similar-shaped PEEK cages.

Secondary outcome measures

SF-36

The SF-36 will be used as the generic quality of life questionnaire (43, 44). The

SF-36 questionnaire has been applied and validated numerous times for intervention studies with back pain and spine surgery. The questionnaire relates to the analysis of the general functional status of patients. The questions are divided in eight domains:

- Physical functioning
- Physical role limitations
- Emotional role limitations
- Social functioning
- Physical pain
- General mental health
- Vitality
- General health perception

Each domain is converted to a 0 to 100 score, a higher score indicating a better health condition. The eight domains are also combined into a physical and psychological summary score. These are converted to range from 0 to 100 with an average person at 50 and a standard deviation of 10 points.

Pain (Back and Leg VAS)

The pain intensity in the back and legs are rated by the patient on a 100 mm horizontal visual analog scale (VAS). The two ends of the scale are "no pain" at 0 mm and "the most terrible pain I can imagine" at 100 mm. The patient is asked to mark the scale based on the average pain intensity during the week prior to the visit to the outpatient clinic. During each visit, the patient will complete one VAS for the pain in either leg, and one VAS for back pain.

Likert score

Recovery is rated by the patient on a 7-point Likert score in which 1 defines complete recovery and 7 is worse than ever. Likert score will be dichotomized in good recovery ('complete recovery' and 'almost complete recovery') and bad recovery ('little

recovery' to 'worse than ever'). Patient will complete the Likert score at the day of discharge from the hospital and during each follow-up visit.

Radiographic Images (Plane radiogram, MRI, CT)
A pre-operative MR and a set of standing plane radiograms of the lumbar spine will be collected for all patients. Pre-operative disc degeneration will be evaluated on the MR scan by the method of Pfirrmann (37). Patient fusion status will be evaluated according to the criteria mentioned by Burkus et al, which are based on qualitative observations (45, 46). Determination of fusion involves the radiographic evaluation of angular changes in spinal alignment, assessment of the device-host interface, and identification of new bone formation and bone remodeling (46). Anterior – posterior radiograms will be collected after 3, 6, 12 and 24 month. After one year, a CT scan (Siemens sensation 16, 3.0 mm slice) of the lumbar spine will be collected to monitor new bone formation and bone remodeling within and around the central core of the cages. Two radiologists will independently analyze the lumbar radiograms and CT. Disagreement between the radiologists will be resolved by consensus.

Complications, adverse events, additional surgery
The investigators will record all complications and adverse events accurately. These will be grouped in the following categories:

- Infections, grouped as superficial wound infections and deep wound infections
- Post-surgical hematoma
- Increased neurological symptoms
- Venous thrombosis
- Other (serious) adverse events

All adverse events and complications will be monitored and followed up until stable or resolved during the course of the study. Each adverse event will be reported to the operating surgeon and will be associated to the type of cage used to qualify the event to be related. Code breaking will occur by the clinical observer or operating surgeon if the clinical condition of the patient necessitates this**.** Early termination of the study will be decided if necessary.

Additional surgery

All additional surgeries during the follow-up period that are related to surgery will be recorded. Any additional spine surgery at the operated level will be considered as a complication and a poor result.

Withdrawal of participants from the trial

A participant may be withdrawn from the clinical study for the following reasons:

- Patients may choose to withdraw from the study under the terms of the Declaration of Helsinki and their consent documentation without having to give a reason
- Any unanticipated adverse reaction which is, in the opinion of the researcher, related to the treatment and will endanger the well-being of the patient if treatment is continued
- The development of any intercurrent illness(es), infection or condition(s) that might interfere with the clinical investigation.
- Non-compliance with the study procedures deemed by the investigator to be sufficient to cause discontinuation
- Any problem deemed by the Investigator to be sufficient to cause discontinuation.

All patients discontinued from the investigation due to an unanticipated adverse reaction, directly related to the investigation, will be treated until the reaction resolves. The researcher will clearly document the date and reason(s) for the patient withdrawal. Patients who have withdrawn from the study will not be replaced if they have received investigation treatment. If possible, any procedures or assessments planned for the patient on withdrawal from the investigation should be performed when intention to withdraw the patient is announced. Patients who are withdrawn prior to receiving treatment will be replaced.

Data management

All data recorded during intake, hospitalization and follow-up visits will be de-identified. Participants will be identified by a unique investigational number (Patient ID number) allocated during intake. Primary and secondary outcome variables, information gathered during intake and hospitalization and all complications, additional surgery, adverse events and withdrawals will be entered by the researcher into an electronic data capture system (Acumen Healthcare Solutions, LLC, Plymouth,

Minnesota, USA). The source documents will be stored in the hospital where the patient underwent the surgical procedure and shall be retained for a period of minimal 5 years after the study completion or longer if deemed necessary.

Statistical considerations

Sample size

The sample size calculation is based on the primary objective to compare the silicon nitride and PEEK cages with respect to improvement in RMDQ score and to demonstrate that the silicon nitride cage is non-inferior to the PEEK cage.

In a large spinal fusion cohort study, Robertson (47) found a mean RMDQ improvement of about 10 points. Scheufler also noted an improvement from a pre-treatment score of 17 to 7 at eight months post-op, with a standard deviation of 4 (48). Both studies included patients with back pain from degenerative disc disease and degenerative spondylolisthesis.

The maximal difference between the treatment arms that could be considered potentially no longer clinically relevant for the RMDQ is thus a difference in improvement of 2 - 3.5 points (39, 41, 49). We therefore consider a non-inferiority margin of 2.6 points between the treatment arms to reflect the maximal difference that is not clinically relevant. Non-inferiority is to be demonstrated based on a one-sided confidence interval with significance level of 2.5% for the difference between the two treatment arms. Assuming a standard deviation of 4 points, 50 patients per arm provide 90% power to demonstrate non-inferiority within a non-inferiority margin of 2.6 points. The total of 100 patients shall be randomized into two groups to minimize bias. This sample size is based on comparing treatment groups with a t-test. The actual analysis is a repeated measurements analysis with baseline as covariate, which is more efficient (requiring less patients, at least about 10% if the correlation between baseline and endpoint is 0.3). Thus, no additional sample size increase is incorporated to account for drop-out. Sensitivity analyses to assess impact of drop outs will be performed.

Statistical Analysis

The primary analysis will be on the change from baseline in RMDQ score. This will be analyzed based on a mixed model for repeated measurements, including baseline RMDQ as covariate and treatment and center as factors. No imputation will be applied for this analysis. The primary comparison will be at 12 months of follow-up. Sensitivity analyses to assess impact of drop outs will be performed. These will include an analysis based on Last Observation Carried Forward imputation, as well as multiple imputations based on differential patterns of drop out / missing data reasons. An exploratory analysis of the distribution of the individual improvements in change from baseline in RMDQ score versus the fusion rate (in three categories) within treatment groups will be performed to assess the extent to which both are consistent. Other continuous outcomes assessed at each visit will be analyzed similarly. Dichotomous outcomes will be compared between treatment groups based on Z-tests for comparing proportions, with results expressed as 95% confidence intervals for the difference in proportions.

Ethical considerations

This study is designed in concordance with the declaration of Helsinki. The protocol has been reviewed and approved by the local medical ethical committee (Verenigde Commissies Mensgebonden Onderzoek). The general board of the participating hospitals also agreed with the protocol. Informed consent will be obtained before participation in this study. Patients are informed they are free to refuse participation. If they choose to participate they may withdraw from this study at any time without comprising further medical care. No financial rewards will be present for patients who agree to participate.

Discussion

PEEK cages are widely used in the treatment of lumbar degenerative disc disorders, and show good clinical results (20, 21). Nevertheless, complications such as subsidence and migration of the cage are frequently seen (22, 23). A lack of osteointegration and fibrous tissues encapsulating PEEK cages are held responsible (24). Ceramic implants made of silicon nitride show better biocompatible and osteoconductive qualities (28-34). Therefore it is expected that the use of silicon nitride cages decrease such complications by better fusion rates. A study design of a double blind multi-center

randomized controlled trial is presented in this article, in which PEEK cages will be compared with silicon nitride cages in the treatment of symptomatic degenerative lumbar disc disorders. Primary objective is to show that treatment with the silicon nitride cage produces similar improvement in RMDQ at all follow-up times compared to the PEEK cage. Total follow-up is 2 years. To our knowledge, this is the first randomized controlled trial in which the silicon nitride cage is compared with the PEEK cage in patients with symptomatic degenerative lumbar disc disorders.

Competing interests

The CORC-mN foundation of the Diakonessenhuis, the Neurosurgical Scientific Partnership The Hague of the Medical Center Haaglanden and Corbin & Company are receiving financial support for their work on this study from Amedica Corporation.

Authors contributions

RK provided research design, writing and project management. SvG provided concept, research design, revision and project management. MA provided project management and revision. KR provided statistical design and analyses. AG provided revision. TC provided concept, research design, statistical design, revision and project management. FÖ provided project management and revision. All authors read and approved the final manuscript.

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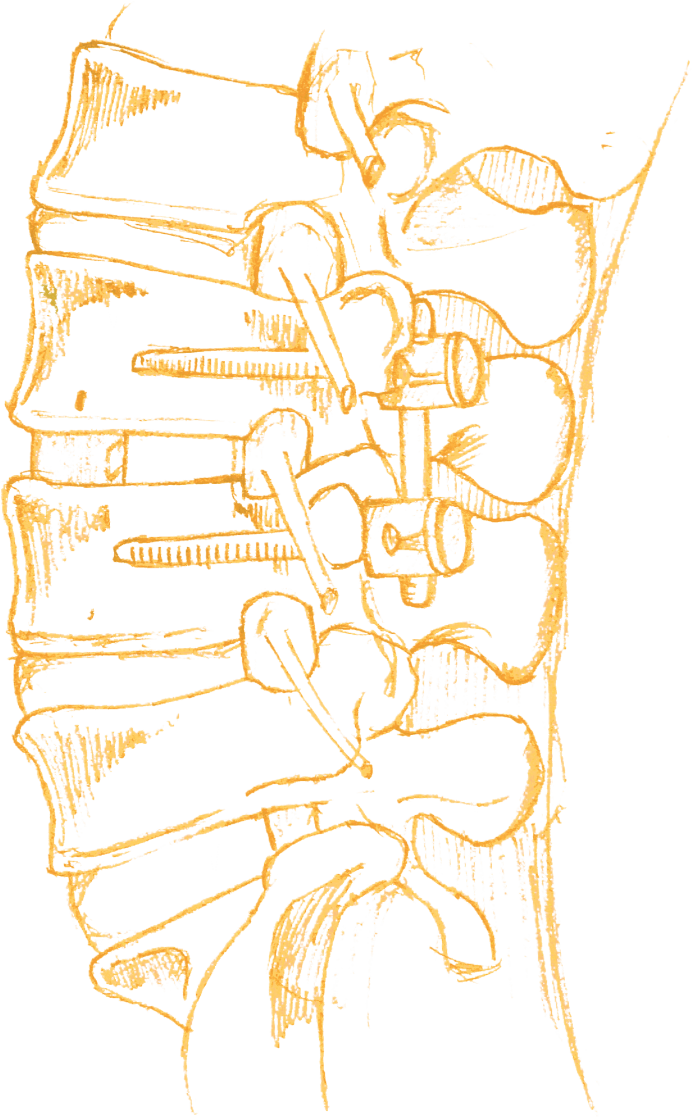

6

THE SNAP TRIAL: TWO-YEAR RESULTS OF A DOUBLE BLIND MULTI-CENTER RANDOMIZED CONTROLLED TRIAL OF A SILICON NITRIDE VERSUS A PEEK CAGE AFTER LUMBAR FUSION SURGERY

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ABSTRACT

Study design: Randomized controlled trial

Objectives: Lumbar interbody fusion with cages is performed to provide vertebral stability, restore alignment, and maintain disc and foraminal height. Polyetheretherketone (PEEK) is commonly used. Silicon nitride (Si3N4) is an alternative material with good osteointegrative properties. This study was designed to assess if Si3N4 cages perform similar to PEEK.

Methods: A non-inferiority double-blind multicenter RCT was designed. Patients presenting with chronic low-back pain with or without leg pain were included. Single- or double-level instrumented transforaminal lumbar interbody fusion (TLIF) using an oblique PEEK or Si3N4 cage was performed. The primary outcome was the Roland-Morris Disability Questionnaire (RMDQ). The non-inferiority margin for the RMDQ was 2.6 points on a scale of 24. Secondary outcomes included the Oswestry Disability Questionnaire (ODI), Visual Analogue Scales (VAS), SF-36 Physical Function, patient and surgeon Likert scores, radiographic evaluations for subsidence, segmental motion, and fusion. Follow-up was planned at 3, 6, 12, and 24-months.

Results: Ninety two patients were randomized (i.e. 48 to PEEK and 44 to Si3N4). Both groups showed good clinical improvements on the RMDQ scores of up to 5-8 points during follow-up. No statistically significant differences were observed in clinical and radiographic outcomes. Mean operative time and blood loss were statistically significantly higher for the Si3N4 cohort. Although not statistically significant, there was a higher incidence of complications and revisions associated with the Si3N4 cage.,

Conclusions: There was insufficient evidence to conclude that Si3N4 was non-inferior to PEEK.

1. INTRODUCTION

Intervertebral fusion is one of the methods to treat chronic low back pain. Mechanical and biological factors play an important role in creating an optimal environment for bony fusion. Originally, stand-alone bone grafts were used, but they are associated with nonunion, collapse and donor side morbidity. Therefore they were succeeded by the use of interbody cages [1]. Interbody cages can be used to restore alignment and maintain disc- and foraminal height while facilitating bony fusion. PEEK has become one of the most frequently used materials with high fusion rates and good clinical results [2]. However, there are also disadvantages. PEEK`s hydrophobic surface discourages direct appositional bone growth, which may lead to the formation of a fibrous layer around the implant [3]. Ti surfaces can be more osteoinductive than PEEK, but they produce artefacts on CT and MRI and are associated with an increased risk of subsidence compared to PEEK [4]. Latest developments focus on combining the two materials to optimize intervertebral fusion. For example, the enhancement of PEEK cages with Ti-coated endplates [5] and hydroxyapatite coated PEEK cages can improve osteointegration [6]. Still, no differences in clinical outcomes and fusion rates are reported between these materials [7].

New materials like ceramics have been introduced. Silicon nitride (Si_3N_4) is such a (non-oxide) ceramic with high strength and toughness. Si_3N_4 minimizes scatter and artefacts on CT and MRI imaging [8]. Due to its surface chemistry it allows a decreased bacterial activity compared to PEEK and Ti [9]. Si_3N_4 received the CE Mark and FDA market clearance for its use as an interbody cage in 2008. It`s mechanical, chemical and osteoconductive qualities were extensively described in literature [10]. A recent animal study showed similar results in mechanical stability and bone formation of Si_3N_4 cages compared to the PEEK [11]. A RCT comparing PEEK and Si_3N_4 cages after anterior cervical discectomy with fusion (ACDF) reported no statistically significant differences in clinical outcome and fusion rates [12]. At the time of our study design, no clinical trial data of Si_3N_4 in the lumbar spine were published yet. Therefore, the Silicon Nitride And PEEK (SNAP) trial was designed to compare a PEEK cage with a Si_3N_4 cage in patients after lumbar fusion surgery [13]. Primary objective was to show that lumbar spinal fusion with a Si_3N_4 cage produces similar improvement in clinical outcome compared to a PEEK cage. This article reports the 2-year outcomes.

2. MATERIALS AND METHODS

2.1 Study design

One hundred patients presenting with chronic low back pain with or without leg pain were treated with either a PEEK or Si_3N_4 cage. The study protocol was published in detail previously [13]. In short, the study was designed as a non-inferiority multicenter clinical observer and patient blinded RCT. Inclusion criteria are listed in table 1. Patients were randomly allocated by use of a centralized 24-hour online computerized randomization system (Sealed Envelope Ltd. London). Measurements were performed pre-operative and at 3, 6, 12 and 24 months.

Table 1: inclusion and exclusion criteria

Inclusion criteria	- Male and female patients age 18-75 years - Chronic low back pain unresponsive to at least six months of conservative care - MRI and standing x-ray evidence of Pfirrmann Grade III or greater disc degeneration and/or degenerative or isthmic spondylolisthesis of Grade I or II - Signed informed consent
Exclusion criteria	- Osteoporosis - Patients with prior failed fusion at the same level - Degenerative scoliosis - Degenerative spondylolisthesis greater than Grade II - Pregnancy - Psychiatric or mental disease - Alcoholism (drinking more than 5 units per day) - Active infection or prior infection at the surgical site - Active cancer - Insufficient language skills to complete questionnaires - Participation in another study - More than two symptomatic levels that need fusion - Planned (e)migration abroad in the year after inclusion

2.2 Ethical considerations

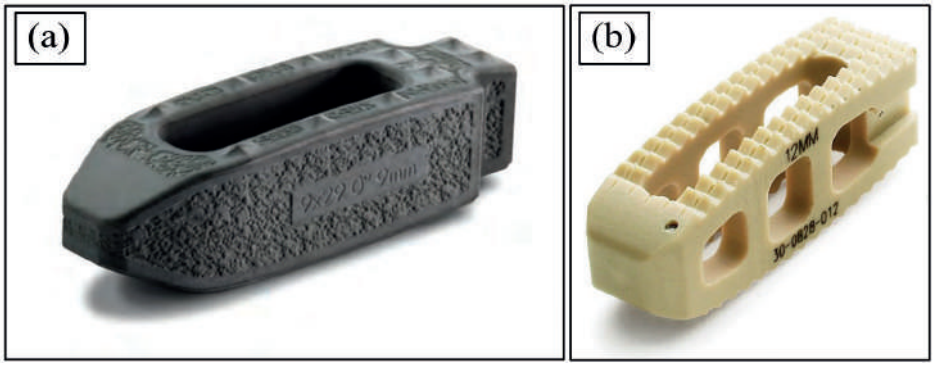
This study was performed in line with the principles of the Declaration of Helsinki. The protocol has been reviewed and approved by the local medical ethics committee (Verenigde Commissies Mensgebonden Onderzoek, as of Jan 1th 2015 known as Medical Research Ethics Committee United, Nieuwegein, the Netherlands. Approval

number NL34808.100.10). Written informed consent was obtained from all individual participants included in the study. Authors were not exempt from requirement.

2.3 Surgical procedure

Single- or double-level transforaminal lumbar interbody fusion (TLIF) with pedicle screw fixation was performed with either an oblique PEEK or Si_3N_4 cage (Phantom™PLIF and Valeo®OL, respectively, CTL Medical, Dallas, TX, USA). (Figure 1 (a) ~ (b)). The Si_3N_4 cage had a lordosis of 0° whereas the PEEK implant had 6° of lordosis. After adequate exposure and placement of pedicle screws, a facetectomy was performed followed by an appropriate decompression on the symptomatic site. The disc space was cleared from disc material and endplates were prepared. Cages were packed with autograft derived from locally harvested bone. A single oblique cage was placed in the prepared disc space. Final fixation of screws and rods was performed under compression. Patients were mobilized on the first day after surgery without bracing.

Figure 1: Lumbar intervertebral cages used in this study: (a) Valeo™ OL Si_3N_4 cage and (b) Phantom™PLIF PEEK cage**.**



2.4 Outcome measures

2.4.1 Clinical assessment

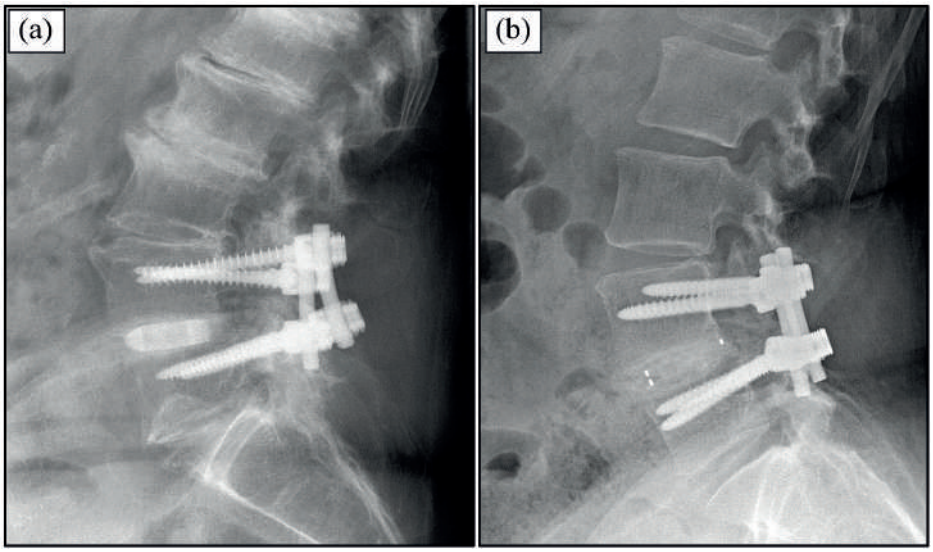
The primary outcome measure was the Roland Morris Disability Questionnaire (RMDQ) (0-24 scale) [14]. Secondary outcome measures included scores from the generic quality of life questionnaire SF-36 [15], Oswestry Disability Index (ODI, 0-50 scale) [16], Visual Analog Scales for leg and back pain (VAS, 0 to 100 mm) [17] and the 7-point Likert score for patient and surgeon perceived recovery in which 'complete

recovery' and 'almost complete recovery' were considered good outcomes [18]. In addition, a neurological examination was conducted at each follow-up.

2.4.2 Radiological assessment

Fusion status was evaluated according to the criteria described by Burkus *et al.* [19]. which included: (i) the presence of bridging bone on a computed tomography (CT) scan (Siemens Sensation 16, Malvern, PA, USA, 3.0 mm slice) at 12-months follow-up; (ii) disc height and angular changes in segmental alignment on lateral conventional radiographs (CR) during follow-up; and (iii) an assessment of device-host interface on a CT scan at 12-months follow-up [19]. Standing anterior-posterior (AP) and lateral CR's were collected at 3, 6, 12, and 24-months of follow-up (figure 2). Average disc heights were determined as the mean of the anterior and posterior measurements. Subsidence was defined as a loss of >1mm in average disc height. At 24-months, additional flexion/extension standing lateral radiographs were obtained to monitor angular motion. Fusion was defined as an angular motion of <2° and translational motion of < 0.5 mm. Each level was analyzed separately in cases with two-level fusion. All radiological analyses were performed by radiologists from an independent organization (Medical Metrics, Houston, TX, USA).

Figure 2. Lateral X-rays of L4-L5 fusion at 24-months for: (a) Si_3N_4 cage and (b) PEEK cage. Note that fusion was achieved with both cage types as indicated by bone bridging between the endplates.



2.5 Statistical analyses

2.5.1 Primary efficacy analysis

The primary outcome was the RMDQ score. Primary objective was to demonstrate that the Si_3N_4 cage was non-inferior to the PEEK cage based on the primary comparison at 12 months. The considered non-inferiority margin was 2.6 points for the difference in RMDQ between the treatment arms [13, 20].The analysis was based on a mixed-effects model for repeated measurements (MMRM). No imputation of missing data was performed. The MMRM model included treatment (type of cage) and center as factors, baseline RMDQ as covariate (fixed effects), and patient as random effect. An unstructured covariance matrix was assumed to model the within-patient variance and estimation was performed by restricted maximum likelihood method. Based on the model, the result of the contrast at 12 months is expressed with point estimate for difference in mean RMDQ between the two cages (Si_3N_4 -PEEK) and one-sided confidence interval with significance level of 2.5%. Non-inferiority was to be demonstrated if the upper boundary of this confidence interval does not exceed the non-inferiority margin of 2.6 points. Assuming a standard deviation of 4 points, 50 patients per arm provide 90% power to demonstrate non-inferiority [13].

2.5.2 Sensitivity analysis

To assess impact of drop outs, sensitivity analysis was performed. This analysis was conducted following Last Observation Carried Forward (LOCF) imputation. The analytical and estimation method for the sensitivity analysis was based on the same mixed-effects model for repeated measurements with the same terms as employed for the primary efficacy analysis (MMRM on the completed dataset).

2.5.3 Secondary efficacy analyses

The secondary efficacy outcomes assessed at each visit (ODI, Vas leg, VAS back, SF36 and radiological measurements) were analyzed using the same mixed-effects model for repeated measurements with the same terms as employed for the primary efficacy analysis. Dichotomous outcomes (dichotomized Likert scales for patient and surgeon perception) were compared between treatment groups based on Z-tests for comparing proportions. Statistical analyses were performed using RStudio and nlme. Plots were created using R base plotting functions and ggplot2.

3. RESULTS

3.1 Baseline characteristics

Between 2012 and 2015, 100 patients were included in two centers (49 and 51). Eight patients were subsequently excluded due to protocol violations (no randomization pre-operative, proof of osteoporosis after inclusion, age during surgery) or cancellation of surgery by the patient after inclusion. Of the remaining 92 patients (46 per each center), 48 were randomized for PEEK and 44 for Si_3N_4. Eight patients in the Si_3N_4 group received a 2-level fusion compared to 5 patients in the PEEK group. Baseline characteristics are shown in Table 2. At 24 months, 7 patients were lost to follow-up (7.6% drop-out rate).

Table 2: Baseline characteristics

	PEEK	Si_3N_4
n	48	44
Age (mean (sd))	53.3 (9.2)	55.4 (11.5)
Gender = Female (%)	33 (68.8)	28 (63.6)
BMI (mean(sd))	27.1 (4.3)	27.1 (5.1)
Smoking = Yes (%)	31 (64.6)	32 (72.7)
Duration of complaints (mean (sd))	10.6 (9.3)	8.9 (6.1)
Type of complaints n(%)		
Radicular pain	8 (16.7)	9 (20.5)
Combination back/radiculair	39 (81.2)	30 (68.2)
Back pain	1 (2.1)	5 (11.4)
Clinical diagnosis n(%)		
Degenerative disc disease	10 (20.8)	13 (29.5)
Isthmic spondylolisthesis grade 1	12 (25.0)	11 (25.0)
Isthmic spondylolisthesis grade 2	5 (10.4)	6 (13.6)
Degenerative spondylolisthesis grade 1	20 (41.7)	14 (31.8)
Degenerative spondylolisthesis grade 2	1 (2.1)	0 (0.0)
Operated levels n(%)		
1-level: L3-L4	4 (8.5)	5 (11.4)
L4-L5	15 (31.9)	11 (25.0)
L5-S1	21 (44.7)	19 (43.2)
L5-L6	1 (2.1)	0 (0.0)
L6-S1	1 (2.1)	1 (2.3)

Table 2: Baseline characteristics (continued)

	PEEK	Si_3N_4
2-level: L3-L5	2 (4.3)	1 (2.3)
L4-L6	0 (0.0)	1 (2.3)
L4-S1	3 (6.3)	5 (11.4)
L5-L6-S1	0 (0.0)	1 (2.3)
RMDQ (mean (sd))	14.2 (4.3)	14.8 (4.3)
ODI (mean (sd))	23.1 (7.4)	22.5 (7.0)
VAS leg (mean (sd))	60.9 (20.7)	58.9 (27.8)
VAS back (mean sd))	62.3 (22.3)	61.7 (21.9)
SF-36 Physical Functioning (mean (sd))	37.0 (19.5)	39.9 (19.4)

3.2 Perioperative results

Peri-operative data are shown in Table 3. There were no differences in length of hospital stay between both groups. Average operative time (Si_3N_4 72-290 min vs PEEK 75 – 240 min) and blood loss (Si_3N_4 120-1700 ml vs PEEK 100-700 ml) was significantly higher in the Si_3N_4 group. There was also a slightly higher peri-operative complication rate in the Si_3N_4 group, although these differences were not statistically significant (table 3).

Table 3: Peri-operative characteristics

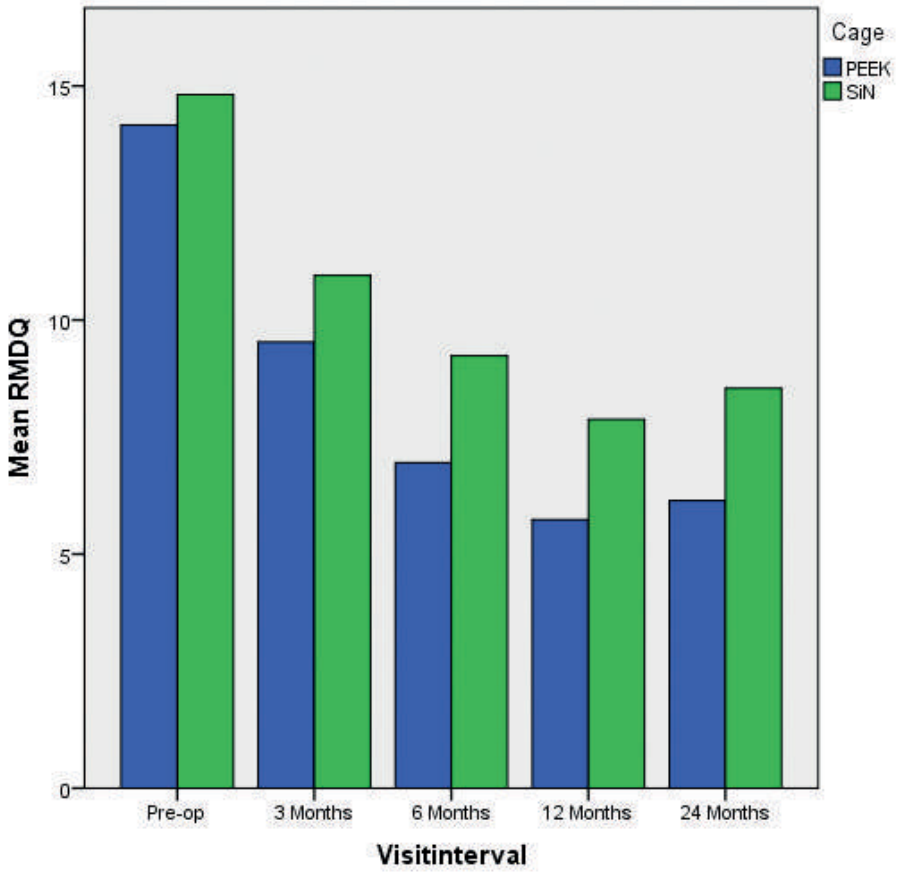
	PEEK (n=48)	Si_3N_4 (n=44)	P value
Operative time min (mean (sd))	127 (46)	150 (51)	0.03*
Blood loss ml (mean (sd))	317 (150)	473 (332)	0.01*
Hospital stay days (mean (sd))	3.8 (2.2)	3.8 (1.6)	0.90*
Complications n (%):			
Dural tear	1 (2.1)	4 (9.1)	0.14**
Implant malposition	0 (0.0)	3 (6.8)	0.07**
Sensory deficit	1 (2.1)	3 (6.8)	0.27**
Motor deficit (MRC grade 4/5)	2 (4.2)	2 (4.2)	0.93**

**Two-sample t-test, p-value for difference 2-sided*
***Two-sample Z-test for equality of proportions, p-value for difference 2-sided*

3.3 Clinical outcome

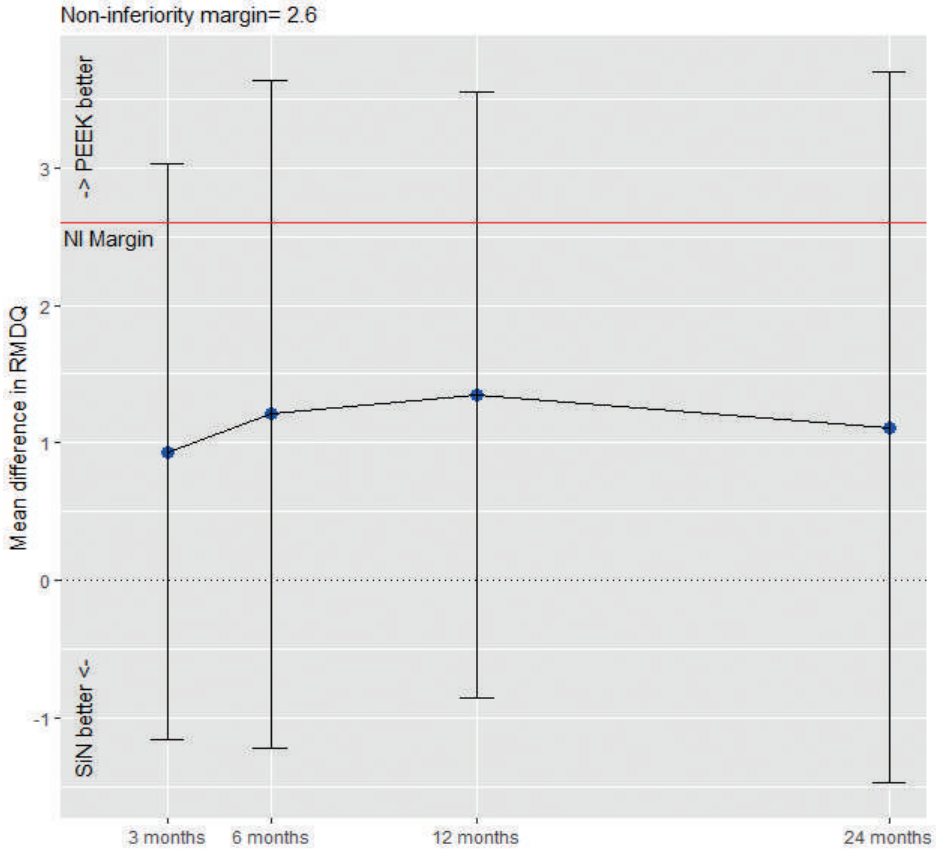
Both treatment arms showed good improvements in RMDQ scores during the 24-months follow-up (figure 3). Although patients treated with PEEK had better outcomes at 3, 6, 12 and 24 months compared to Si_3N_4, these differences were not significant.

Figure 3: RMDQ scores during follow-up



Using the a priori selected non-inferiority margin of 2.6, the null hypothesis that Si_3N_4 is non-inferior to PEEK could not be rejected. This is graphically shown in figure 4. The upper boundary of the confidence interval exceeds the non-inferiority margin of 2.6 at each follow-up period.

Figure 4: 95% CI of RMDQ difference between PEEK and Si_3N_4 by visit interval.



Secondary outcomes are shown in table 4. All patients showed good improvements during follow-up. There were no significant differences in VAS leg, VAS back, SF36 and ODI scores between the two groups. Although both surgeons and patients reported generally better recovery rates for the PEEK group at each follow-up time point, these differences did not reach statistical significance.

Table 4: Outcome during follow-up

	PEEK	Si_3N_4	p value
Roland Morris Disability Questionnaire (sd) 0-24 scale			
3 months	9.5 (5.5)	11.0 (5.2)	0.19*
6 months	7.0 (6.3)	9.2 (6.7)	0.16*
12 months	5.7 (5.8)	7.9 (6.4)	0.11*
24 months	6.1 (6.5)	8.5 (7.0)	0.20*
Oswestry Disability Questionnaire (sd) 0-50 scale			
3 months	14.8 (9.4)	15.7 (8.0)	0.47*
6 months	10.7 (10.3)	12.3 (8.7)	0.49*
12 months	10.2 (10.2)	9.7 (9.1)	0.17*
24 months	11.9 (10.3)	11.2 (10.9)	0.40*
VAS leg (sd) 0-100 scale			
3 months	26.5 (27.7)	26.4 (26.2)	0.49*
6 months	23.6 (29.2)	26.2 (28.8)	0.47*
12 months	24.6 (28.4)	26.5 (22.9)	0.28*
24 months	26.3 (25.3)	30.0 (31.3)	0.31*
VAS back (sd) 0-100 scale			
3 months	34.9 (18.1)	37.9 (22.3)	0.49*
6 months	28.9 (23.3)	26.4 (25.4)	0.27*
12 months	30.2 (21.9)	31.0 (22.9)	0.39*
24 months	34.8 (24.7)	38.2 (25.7)	0.45*
SF36 physical functioning (sd)			
3 months	59.2 (20.6)	58.0 (17.2)	0.44*
6 months	66.0 (23.9)	61.2 (19.7)	0.25*
12 months	73.1 (23.1)	68.5 (21.2)	0.24*
24 months	71.5 (24.6)	64.9 (23.0)	0.20*
Surgeon perceived Likert (%)			
3 months	73.3	58.1	0.20**
6 months	76.2	61.0	0.20**
12 months	78.6	61.9	0.15**
24 months	78.0	56.3	0.08**
Patient perceived Likert (%)			
3 months	64.3	58.1	0.72**
6 months	76.2	56.1	0.09**
12 months	78.6	64.3	0.23**
24 months	75.0	50.0	0.05**
Disc height (mm)			
postoperative	8.3	8.1	0.63*
3 months	7.3	7.3	0.91*
6 months	7.2	7.0	0.67*
12 months	7.1	6.9	0.67*
24 months	7.1	6.9	0.68*
Translational motion (mm) 24 months	0.12	0.14	0.70**
Angular motion (°) 24 months	0.94	1.18	0.24**

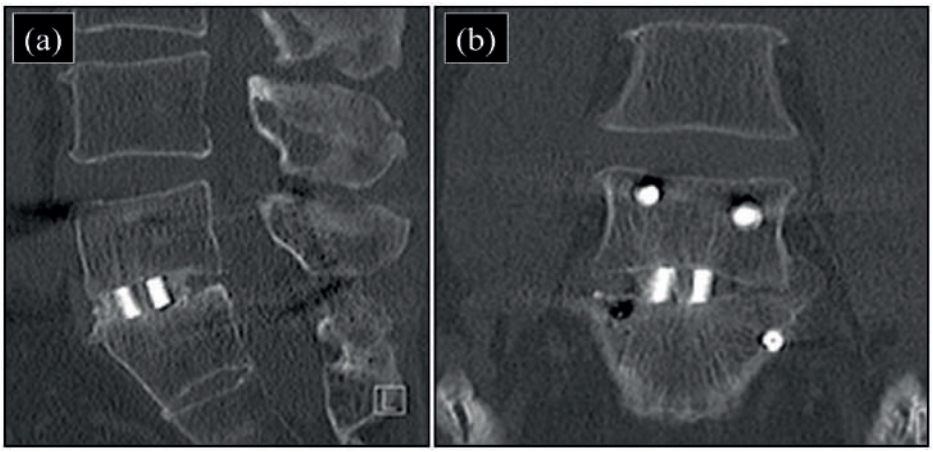
** estimated from an MMRM model with the same specification as for the primary outcome analysis, p-value for difference one-sided*

***Two-sample t-test, p-value for difference 2-sided*

3.4 Radiological outcomes

The radiographic data are also provided in Table 4. There were no significant differences in average disc heights between groups. Also, no significant differences in fusion rates were seen between the PEEK and Si_3N_4 based on the flexion/extension analysis of angular or translational motion (88% vs 82% respectively, p=0.40). Bony bridging, measured on CT at 12 months, was seen in 42% vs 57% of patients in the PEEK and Si_3N_4 group respectively (p=0.13). Sagittal and coronal views for a Si_3N_4 implant are shown in Figure 5 (a)~(b). Due to the fact that PEEK cages are radiolucent, the interface between the endplates and these cages could not be adequately ascertained. An assessment of the device-bone interface (*i.e.*, radiolucency or osseous integration) was therefore deemed to be unreliable and could not be incorporated into the analyses.

Figure 5. CT imaging of a Si_3N_4 cage at 12 months, showing bridging in the (a) sagittal and (b) coronal views. No signs of lucency were seen at the device-bone interface.



3.5 Complications and revisions

During 24 months follow-up there were 14 revisions (15.2% revision rate). Specifications are provided in table 5. In the PEEK group 4 out of 48 patients (8.3%) were revised, compared to 10 out of 44 patients (22.7%) in the Si_3N_4 group (p=0.10). Almost one third of revisions were performed due to adjacent level problems (5 out of 14).

Table 5: Revision surgery

Cage	Index level	Time	Revision
PEEK	L4-S1	5 months	redecompression L5-S1
PEEK	L5-S1	7 months	redecompression L5-S1 + screw removal S1
PEEK	L4-L5	10 months	adjacent level L5-S1
PEEK	L3-L4	14 months	adjacent level L4-S1
Silicon Nitride	L5-S1	1 day	revision cage due to implant malposition
Silicon Nitride	L5-S1	2 days	revision screw L6 due to neurological disorder
Silicon Nitride	L5-S1	6 months	revision screw due to lose endcap
Silicon Nitride	L5-S1	7 months	redecompression L5-S1
Silicon Nitride	L4-S1	8 months	adjacent level L3-L4
Silicon Nitride	L3-L4	10 months	adjacent level L4-S1
Silicon Nitride	L5-S1	18 months	revision cage due to non-union/loosening screws
Silicon Nitride	L5-S1	18 months	revision cage due to loosening cage
Silicon Nitride	L3-L4	19 months	adjacent level L4-L5
Silicon Nitride	L5-S1	20 months	revision cage due to non-union.

4. DISCUSSION

The SNAP trial was designed to compare the clinical and radiological outcomes for Si_3N_4 cages versus PEEK cages in patients undergoing lumbar fusion surgery. The overall results indicate that patients treated with either cage material had comparable outcomes with respect to disability, pain, and fusion. In particular, the RMDQ improvements observed in this trial were in line with the results from other spinal fusion studies [21, 22], thereby reflecting good two-year clinical outcomes for both groups. The secondary outcome scores were also consistent with reported literature using PEEK cages, ranging from 24 to 36 for VAS back pain, 26 to 42 for VAS leg pain [2] and 9 to 20 for ODI [23]. Lastly, the fusion results observed were also found to be similar to values reported in literature [2].

4.1 Primary outcome

In this study, it was hypothesized that Si_3N_4 would be non-inferior to PEEK as measured by a non-inferiority margin of 2.6 points on RMDQ scores at 12-months follow-up. Although both implant groups had improvement scores of up to 5-8 points, there was insufficient evidence to conclude that Si_3N_4 was non-inferior to PEEK. As with any non-inferiority study, this does depend directly on the non-inferiority margin of 2.6 points improvement on RMDQ that was pre-determined**.** Our considerations are part of the protocol [13], but other perspectives could have been taken. For example, Stratford et al [24] reported that the minimum detectable difference between pre- and post-treatments in patient with low back pain varied based on the patient's initial RMDQ score. They concluded that clinically important changes in the RMDQ were 2 (for an initial score of 0 to 8), 4 (for an initial score of 5 to 12), 5 (for an initial score of 9 to 16), 8 (for an initial score of 13 to 20), and 8 (for an initial score of 17 to 24). Since in our study the initial RMDQ score was 14, a higher non-inferiority margin might have been chosen, although such a margin does not only depend on the minimal detectable difference at individual patient level. It does stress the importance of stratification of the patient population in assessing relevant pain scores, and should be taken into consideration for future studies.

4.2 Perioperative outcomes

A significant difference was found in operative time and blood loss in favor of the PEEK cohort (*i.e.*127 min vs 150 min and 317 ml vs 473 m respectively). The greater amount of blood loss was directly linked to a longer operative time for the Si_3N_4 cohort. However, this result is skewed due to an outlier value of one patient in the Si_3N_4 group whose blood loss was 1700 ml. The difference in operative time can also be partially explained by a higher number of 2-level procedures in the Si_3N_4 cohort compared to PEEK (*i.e.*, 8 versus 5). Additionally, upon rotating the Si_3N_4 cage during insertion, in two patients a fracture occurred at the insertor-cage interface. These cages needed to be replaced, extending the operative time. After thorough analysis, the cause of these two incidents was found to be a lack of stability in the insertor-cage interface. After adjusting the tip of the insertor, which created a more stable grip while inserting the cage, no additional fractures occurred. Other perioperative complications were evenly distributed over the length of the study.

4.3 Radiological outcomes

There is considerable controversy in the scientific literature as to when a lumbar segment is radiologically fused [19, 25]. Various criteria of angular and translational motions have been proposed, coupled with the presence of anterior bridging bone (*i.e.*, the "sentinel sign") without radiolucencies at the superior or inferior surfaces of the implant. In this study, as the PEEK cages were radiolucent, an assessment of either radiolucencies around these cages and their osseous integration was deemed unreliable and therefore unusable for this analyses. However, several other criteria were usable. First, bony bridging was measured on CT at 12 months and defined as the presence of a bony bridge from one endplate to the next. Secondly, disc height measurements were used for analyses of potential subsidence. In both groups no statistically significant differences were seen in average amount of subsidence or bony bridging. Thirdly, segmental motion measured on flexion/extension radiograms was used to analyze fusion, defining angular motion < 2° and translational motion < 0.5 mm as fusion. This study showed fusion rates consistent with results found in literature [2]. However, a technically and/or radiographically insufficient fusion does not necessarily equates an unsuccessful clinical outcome because vertebral stability may occur before it is radiographically evident [26]. That can explain that there is no clear evidence that a bony fusion correlates with a good clinical outcome.

4.4 Complications

There were more revisions within the Si_3N_4 group compared to the PEEK group (10 vs 4), however this difference was not statistically significant (p=0.10) (table 5). Most revisions were performed due to adjacent level problems. Also, as described earlier, two Si_3N_4 cages fractured during surgery at the insertor-cage interface due to a technical problem with the insertor.

4.5 Limitations

The design of the SNAP trial had several limitations. Firstly, the use of a single oblique cage was chosen to allow for more accurate fusion measurements on CT. However, a single cage is mechanically less stable compared to 2 parallel placed cages [27]. This could have biased the results and can also explain the high revision rate of 15.2%. Secondly, as discussed earlier we can reiterate the way our non-inferiority margin of 2.6 points improvement on RMDQ was determined. Thirdly, this study was

funded by Amedica Corporation (Salt Lake City, UT, USA), the manufacturer of the Si_3N_4 cage. Every effort was made to eliminate bias in the study design, protocol, and management of the study. Independent Clinical Research Organization (CRO) managed the study together with the principal investigator's institution, the statistical analyses were performed by an independent organization employing their own statisticians (Julius Centre for Health Sciences and Primary Care, University Medical Center Utrecht, The Netherlands) and yet another independent unit performed the radiographic measurements (Medical Metrix). With those precautions, the authors have implemented the most reasonable procedure to minimize bias.

5. Conclusions

Despite the fact that both groups in our trial had good clinical improvements on the RMDQ scores during follow-up of up to 5-8 points after 24 months, there is insufficient evidence to conclude that the Si_3N_4 cage is non-inferior to the PEEK cage. Perioperative blood loss and surgery time were significantly higher in the Si_3N_4 group. Additionally, a higher incidence of complications and a higher incidence of revisions seemed to be associated with the Si_3N_4 cage, although not statistically significant.

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PART III.

CHALLENGES IN THERAPEUTIC STRATEGIES AND OUTCOME MEASUREMENT

7

TEMPORARY SEGMENTAL DISTRACTION AS A TREATMENT FOR A DOG WITH DEGENERATIVE LUMBOSACRAL STENOSIS

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ABSTRACT

Objectives: Degenerative lumbosacral stenosis (DLSS) is characterized by intervertebral disc degeneration and causes lower back pain in dogs. Temporary distraction in rabbit models with induced intervertebral disc degeneration showed signs of inter- vertebral disc repair. In the present study, we assessed safety and efficacy of temporary segmental distraction in a dog with clinical signs of DLSS

Methods: Distraction of the lumbosacral junction by pedicle screw–rod fixation was applied in a 5-year-old Greyhound with DLSS and evaluated by radiography, magnetic resonance imaging, and force plate analysis before and after distraction.

Results: Safe distraction of the lumbosacral junction was demonstrated, with improvement of clinical signs after removal of the distraction device. Signal intensity of the intervertebral disc showed no changes over time. T2 value was highest directly after removal of the distraction device but decreased by 10% of the preoperative value at 9 months of follow-up. Disc height decreased (8%) immediately after removal of the distraction device, but recovered to the initial value. A decrease in the pelvic/thoracic propulsive force during pedicle screw–rod fixation and distraction was demonstrated, which slowly increased by 4% compared with the initial value.

Clinical significance: Temporary pedicle screw–rod fixation in combination with distraction in a dog with DLSS was safe, improved clinical signs and retained disc height at 9 months of follow-up.

Introduction

Degenerative lumbosacral stenosis (DLSS) is a well- described disorder in medium and large breed dogs which can manifest in patients as signs of lower back pain, lameness and neurological deficits.[1] It is a disorder of multifactorial origin, in which intervertebral disc degeneration and hernia- tion (Hansen type II) play an important role.[1] A loss of physiological tension within the intervertebral disc may lead to segmental instability and proliferation of osseous and soft tissues, resulting in spinal stenosis and compression of the cauda equina. Surgical treatment consists of decompression of neural tissue, and in cases with instability, fixation and fusion of the lumbosacral junction can be performed.[1–3] Nevertheless, none of the current treatments restore the functional integrity of the intervertebral disc.

A relatively new approach to cartilage regeneration of osteoarthritic joints is temporary distraction, which origi- nates from the field of osteoarthritis in the human ankle and knee.[4–6] Although the exact underlying mechanism is not known yet, distraction reduces the mechanical stresses on the cartilage, prevents further wear and tear of the cartilage surfaces and allows chondrocytes to initiate repair. Because of the similarities between articular cartilage and the inter- vertebral disc, several experimental studies have focused on segmental distraction of the intervertebral disc to provide optimal conditions for regeneration.[7] Distraction of both the intervertebral disc and facet joints can be achieved by using a pedicle screw–rod fixation device.[2,8] Nevertheless, fixation of a spinal segment alters the biomechanics of the spinal column, and secondary pathology such as adjacent segment disease and facet joint pathology are possible complications if the constructs remains in situ for a longer period.[9] Placing a fixation and distraction device temporarily could allow biological repair of the affected intervertebral disc and might prevent adjacent segment changes. In several in vivo rabbit intervertebral disc degeneration models, distraction of the intervertebral disc showed signs of tissue repair at a biological, cellular and biomechanical level.[10] To our knowledge, the effect of temporary intervertebral disc distraction in animals with spontaneous intervertebral disc degeneration has not been evaluated before. Therefore, we assessed the safety and efficiency of temporary distraction in a dog with clinical signs of spontaneous intervertebral disc degeneration.

Clinical Case

A 5-year-old, 31 kg, intact male Greyhound was presented because of signs of lower back pain. The dog showed a slight kyphosis of the vertebral column, a shortened and stiff stride of the pelvic limbs, signs of pain on palpation of the lumbosacral junction and a painful response to the lumbosacral extension test. Orthogonal radiographs of the lumbosacral area were obtained under sedation (t_{-1}) and showed minimal mineralization of the sixth lumbar (L6) to seventh lumbar (L7) intervertebral disc. Magnetic resonance (MR) images (T1-weighted [T1W], T2W, T2 maps) of the lumbosacral area were obtained under general anaesthesia (t_{-1}) using a 1.5-Tesla scanner and a Sense NeuroVascular 16 top-off coil (Phillips Healthcare, Best, The Netherlands) according to the protocol previously described.[11] On the sagittal planes, a mild protrusion at the L7–first sacral (S1) disc space was seen, and slight degeneration of the fourth lumbar (L4)–fifth lumbar (L5) and L7–S1 intervertebral discs was noted. The dog was treated with carprofen (2 mg/kg PO every 12 hours). As the dog showed no signs of improvement on medical treatment, temporary distraction of the lumbosacral segment was performed (t_0). All procedures were approved and conducted in accordance with the guidelines set by the Animal Experiments Committee of Utrecht University (experimental number: 2012.III.03.029), as required by the Dutch regulation.

Methods

Temporary distraction of the lumbosacral junction by pedicle screw–rod fixation under general anaesthesia was applied by a board-certified veterinary surgeon (BPM) and orthopaedic surgeon (FCÖ). The surgical procedure and insertion of the pedicle screws are described in detail by Smolders and colleagues.[12] Four 25-mm long, 4-mm wide titanium pedicle screws (USS Small Stature; DePuy Synthes, Zeist, The Netherlands) were inserted into the pedicles and vertebral bodies of L7 and S1 under fluoroscopy. Two 5-cm long, 6-mm wide titanium rods (USS Small Stature) connected the L7 pedicle screws with the two ipsilateral S1 pedicle screws. The rod was slightly adjusted with a rod bender (USS Small Stature) to acquire optimal alignment with both screw heads. Prior to tightening of the sleeves and nuts on the screw heads, 5-mm distraction[4] was applied with a Gelpi distractor to the pedicle screws over the

L7–S1 junction. A part of the cauda equina was exposed due to partial rupture of the ligamentum flavum; hence, a splash block of morphine (Morphine; Centrafarm, Etten-Leur, The Netherlands; 0.1 mg/kg in 2 mL of 0.9% NaCl) was given and a small epidural autologous free fat graft was placed.

Distraction was applied for 3 months, based on studies in humans with severe osteoarthritis of the ankle.[6] After 3 months, the pedicle screw–rod formation was removed in a second surgery (t_3). During removal of the four pedicle screws, it was noticed that the L7 pedicle screws were more firmly seated in the bone than the S1 pedicle screws. A swab was obtained from a screw hole in the sacrum and submitted for bacteriology. Follow-up times for radiography, force plate analysis, disc height index (DHI) and MR images are depicted in ►Table 1. Disc height index was calculated for L7– S1 on radiographs.[13] The surface area of the intervertebral disc was measured at all-time points on lateral radiographs using Adobe Photoshop CS6 (Adobe Systems; San Jose, California, United States) thereby using the length of the vertebral body L7 as a reference. Intervertebral disc degeneration grades were evaluated on mid-sagittal slices of T2W images according to the Pfirrmann classification.[14] T2 mapping values were calculated and analysed according to a previously described method.[11] Force plate analysis was performed by measuring ground reaction forces (peak vertical force [Fz^b], peak braking forces [Fy^b] and peak propulsive forces [Fy]).[15]

Table 1. Follow-up schedule

Time	Time point (t_{month})	Radiographs	Force plate analysis	MRI
Preoperatively	t_1	Yes	Yes	Yes
At placement of distraction device	t_0	Yes	No	No
At removal after 3 months of distraction	t_3	Yes	Yes	Yes
3 months	t_6	Yes	Yes	No
9 months	t_9	Yes	Yes	Yes

Abbreviation: MRI, magnetic resonance imaging.

Results

Placement of Pedicle Screw–Rod Fixation and Distraction (t0)

After placement of the pedicle screw–rod fixation device, the dog was admitted to the surgical ward and treated intravenously (IV) with fentanyl (Fentanyl; Bipharma, Hameln Pharmaceuticals, GmbH, Gloucester, United Kingdom; 4 µg/kg/h IV), ketamine (Ketamine; Vétoquinol, Lure Cedex, France; 4 µg/kg/min IV), carprofen (Carprofen; AST Farma, Oudewater, The Netherlands; 4 mg/kg IV) and amoxicillin/clavulanic acid (Amoxicillin/clavulanic acid; Sandoz GmbH, Kundl, Austria; 20 mg/kg every 8 hours). The fentanyl/ketamine was tapered down the next day and after methadone (Methadone; Eurovet Animal Health B.V., Bladel, The Netherlands; 0.2 mg/kg IV) was given once, oral tramadol (Tramadol; Centrafarm, Etten-Leur, The Netherlands; 3 mg/kg PO every 8 hours) wasstarted. The dog was clinicallyevaluated daily by a veterinarian (NW), and pain was assessed according to the short form of the Glasgow composite pain scale. One day after surgery, swelling at the level of the popliteal lymph nodes of both stifles was noticed, most likely associated with congestion or local bleeding. Four weeks after insertion of the pedicle screw–rod fixation distraction device, the dog showed mild kyphosis and stiffness of the caudal lumbar area, less severe than at the initial clinical examination (t_{-1}). Radiographs of the lumbosacral area showed no abnormalities. The dog was treated with carprofen (4 mg/kg PO every 24 hours) for 14 days. The dog's activity was restricted for 6 weeks and was only allowed to walk on a leash for 10 to 15 minutes four times a day.

Removal of Pedicle Screw–Rod Fixation (t3)

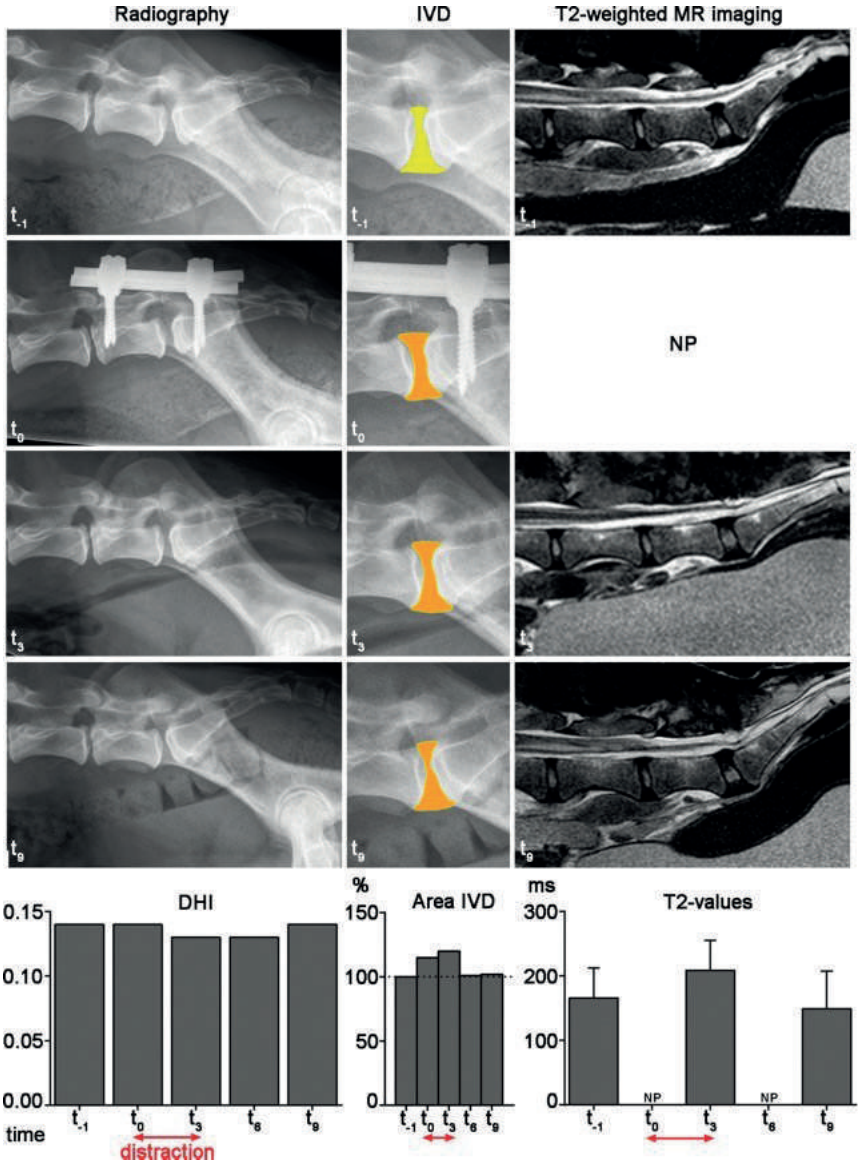
After removal of the pedicle screw–rod fixation device, the dog was admitted to the surgical ward and was treated IV with dexmedetomidine (Dexmedetomidine; Vétoquinol, Lure Cedex, France; 1 µg/kg/h IV for 24 hours, buprenorphine Buprenorphine; AST Farma, Oudewater, The Netherlands; 20 µg/kg IV every 6 hours) for 2 days, and orally with carprofen (4 mg/kg PO every 24 hours) for 10 days. After the buprenorphine was stopped, tramadol (3 mg/kg PO every 8 hours) was started and given orally for 14 days. Again, the dog's activity was restricted for 6 weeks, and was only allowed to walk on a leash for 10 to 15 minutes four times a day. Recovery after implant removal was uneventful. The bacteriology swab tested negative. Clinical examinations during the follow-up period showed no pain response to superficial

palpation and only a mild response to deep palpation of the lumbosacral joint. Rescue analgesic intervention was not needed.

Radiographs

Radiographs obtained during or after distraction showed no evidence of implant failure or migration. Disc height index in L7–S1 remained unchanged after distraction (t_{-1} vs t_0) (►Fig. 1). At 3 months of distraction, immediately after removal of the device (t_3), and at 6 months (t_6), DHI decreased by 8%. At 9 months (t_9), the DHI returned to the initial value (t_0). Although the DHI was not different before and after distraction (t_{-1} vs. t_0), assessment of the complete intervertebral disc revealed distraction of the dorsal part of the intervertebral disc and compression of the ventral part (►Fig. 1). The intervertebral disc surface area on lateral radiographs increased by 15% and 20% at t_0 and t_3, respec tively, compared with t_{-1}. At 6 (t_6) and 9 (t_9) months, the intervertebral disc surface area decreased to values slightly higher, that is 1% and 2%, respectively, than the initial value at *t*-1.

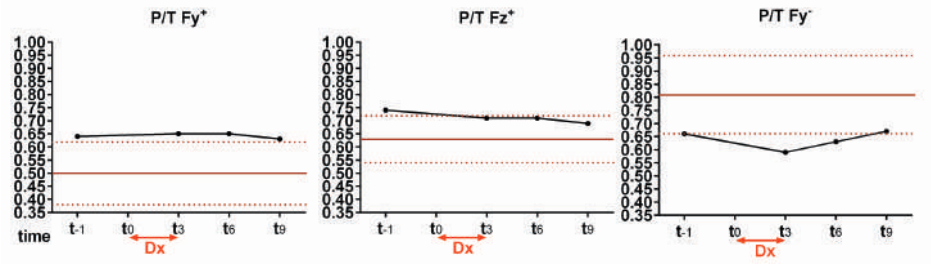
Figure 1. Lateral radiographs and lateral T2W magnetic resonance images of the lumbosacral junction of a dog with degenerative lumbosacral stenosis exhibiting lower back pain and concurrent mild degeneration of the L7–S1 IVD. Temporary distraction of the lumbosacral junction was applied with the aid of pedicle screw-rod fixation. The dog was evaluated at the following time points: before (t-$_1$), directly after application of the distraction device (t_0), after 3 months of distraction at removal of the device (t_3), and again at 6 (t_6) and 9 months (t_9) of follow-up. DHI and area of the IVD were measured on lateral radiographs, with t-$_1$ set at 100%. *T2* values are mean (±SD) *T2* mapping values in the NP, obtained at the same time as the T2W images. DHI, disc height index; IVD, intervertebral disc; NP, not performed; SD, standard deviation; T2W, T2-weighted.



Force Plate Analysis

Before distraction, the pelvic/thoracic (P/T) peak vertical force (Fz^{b}) and P/T peak braking force (Fy^{b}) were slightly higher than reference values in control animals, whereas the P/T peak propulsive force (Fy) ratio was comparable with that in dogs with DLSS as described by Suwankong and colleagues (►Fig. 2).[16] A decrease of 16% of the P/T Fy was noticed after 3 months of distraction. The P/T Fy slowly increased after the distraction device was removed and resulted in a value at 9 months follow-up that was 4% higher than the initial preoperative P/T Fy value.

Figure 2. Line curves of the pelvic/thoracic ratio of the braking force (Fyþ), vertical force (Fzþ) and propulsive force (Fy-) in a dog with degenerative lumbosacral stenosis, in which pedicle screw-rod fixation in combination with temporary distraction was applied. The dog was evaluated at the following time points: before (t-$_1$), directly after application of the distraction device (t_0), at removal of the device after 3 months of distraction (t_3), and again at 6 (t_6) and 9 months (t_9) follow-up.



Discussion

Safe temporary fixation and distraction of the lumbosacral intervertebral disc and facet joints by using pedicle screw– rod fixation was demonstrated in a dog with clinical signs due to DLSS with early intervertebral disc degeneration. Signal intensity of the intervertebral disc on T2W MR images during and after temporary static distraction remained unchanged. Furthermore, the T2 mapping value, a quantitative MR imaging parameter shown to be more sensitive in detection of qualitative changes over the course of intervertebral disc degeneration, was highest directly after removal of the distraction device, indicative of an increase in water content,[17] but decreased by 10% at 9 months follow-up compared with the preoperative value. Despite the initial increase in the T2 mapping value, DHI slightly decreased (8%) after removing the distraction device but recovered to the preoperative value at 9 months follow-

up. Nevertheless, precision of these results could not be indicated in only one dog. Tellegen and colleagues recently published a translational study in which client-owned dogs with chronic back pain were treated with a local drug delivery system releasing celecoxib, a COX-2 inhibitor.[18] These client-owned dogs were large breed dogs within the same body size and weight range as the dog in the present study. In these dogs, T2 maps were generated with the same protocol as described in this case report. The T2 mapping values in non-injected discs in those dogs showed a maximum variation in measurements of 15%. T2 map values in our case report increased by 21% after distraction, but eventually decreased by 11% compared with the reference value at t_0. Based on these numbers, we cannot rule out that the T2 mapping values in this one individual dog reflect a physiological variation instead of a change related to the treatment.

The fibrotic changes of the facet joints at both levels may be caused by the operative trauma, immobilization of these joints during the distraction period, an increase in biomechanical loading after removal of the static unloading device or some combination of these factors. As shown in people, shortening of the distraction period to 4 or 6 weeks might reduce formation. Furthermore, a shorter period most likely has similar regenerative effects, as biomarker-turnover of cartilage and bone tissue increases within the first 4 weeks of joint distraction, and thereafter stabilizes.[19]

In a rabbit intervertebral disc compression model resulting in a decreased signal intensity of the intervertebral disc on MRI, temporary dynamic distraction showed re-establishment of the physiological signal intensity on MRI. Contrasting findings between the dog and the rabbit model were observed due to several aspects. First, the type of distraction device differed in both animal studies, that is static in the dog, versus dynamic in the rabbit model. Dynamic loading has been shown to maintain the balance between anabolic and catabolic pathways within the extracellular matrix.[20] In a more static loading condition, decreased nutrient supply might have limited extracellular matrix synthesis, resulting in a lower expression of water-binding proteins, and a consequently lower signal intensity on T2W MRI. Furthermore, pins in the rabbits were placed perpendicular to the spinal segments. Pedicle screws in the dog could not be placed strictly perpendicular, due to anatomical limitations and safe pedicle corridors,[11] eventually resulting in distraction of the dorsal, but compression

of the ventral part of the intervertebral disc space. Finally, differences in genetic background between rabbit and dog, or the stage of intervertebral disc degeneration or a combination of both may have contributed to the difference.

Dogs with DLSS have decreased propulsive forces of the hindlimbs (P/T Fy ratio).[16] The initial decrease in the P/T Fy in this dog during pedicle screw–rod fixation and distraction is in line with findings in literature,[2,12] and is most likely associated with a reduction in pelvic limb muscle strength and volume within the rehabilitation period. Shortening of the distraction period might decrease post-treatment stiffness and may reduce this initial decrease in P/T Fy , and/or accelerate improvement. In previous in vivo dog studies, the P/T Fy ratio initially decreased after fixation of the lumbosacral joint by using pedicle screw–rod fixation at 6 and 12 weeks, but increased at 6 months after surgery.[2,12] Interestingly, the propulsive forces of the dog also improved 9 months after the removal of the pedicle screw–rod fixation distraction device. A longer follow-up time is needed to give more insight into the long-term outcome.

A commercially available pedicle screw–rod fixation device was used that is designed to fixate a spinal segment permanently. Two limitations of such a device are the unquantified amount of distraction applied during surgery, and a relatively invasive insertion and removal procedure. Distraction of stifle joints in dogs,[4] and intervertebral discs in rabbits,[21] has been performed using external fixators. In this procedure, an external device, including a calibrated spring, serves as a distractor and is attached to bone pins that are placed on either side of the joint under fluoroscopic guidance. By using a spring, a constant controllable dynamic decompression over the entire unloading time can be established, and all implants can be removed via a minimal invasive surgical procedure. Currently, none of the aforementioned devices are commercially available, and need to be customized for the canine spine.

The current study is a pilot study investigating the application of temporary distraction as a treatment for lower back pain related to intervertebral disc degeneration, in a similar way as distraction has been used to treat degenerative osteoarthritis.[4–6] At this moment, clinical efficacy of the distraction technique for lower back pain has not been proven, the technique remains technically challenging as described in a recent article where the implants were used for permanent fixation and distraction[22]

and a second surgery is needed to remove the implants. Also, there is a need for implant development for temporary distraction. Therefore, this pilot study needs to be interpreted with care; it is a starting point, but its clinical efficacy needs to be investigated in future studies with longer follow-up times and more patients.

Funding

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Conflict of Interest

None.

Author Contributions

SMvG, FCÖ, MAT and BPM participated in the study conception. All authors were involved in the study design and acquisition, analysis and interpretation of data, and in the drafting and revision of the manuscript. All authors have read and approved the final manuscript.

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8

SURGICAL RESTORATION OF SAGITTAL ALIGNMENT OF THE SPINE: CORRELATION WITH IMPROVED PATIENT-REPORTED OUTCOME. A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Background: The sagittal-plane curvatures of the human spine are the consequence of evolution from quadrupedalism to bipedalism and are needed to maintain the center of mass of the body within the base of support in the bipedal position. Lumbar degenerative disorders can lead to a decrease in lumbar lordosis and thereby affect overall alignment of the spine. However, there is not yet enough direct evidence that surgical restoration of spinal malalignment would lead to a better clinical outcome. Therefore, the aim of this study was to assess the correlation between patient-reported outcomes and actual obtained spinal sagittal alignment in adult patients with lumbar degenerative disorders who underwent surgical treatment.

Methods: A comprehensive literature search was conducted through databases (PubMed, Cochrane, Web of Science, and Embase). The last search was in November 2018. Risk of bias was assessed with the Newcastle-Ottawa quality assessment scale. A meta-regression analysis was performed.

Results: Of 2,024 unique articles in the original search, 34 articles with 973 patients were included. All studies were either retrospective or prospective cohort studies; no randomized controlled trials were available. A total of 54 relations between preoperative-to-postoperative improvement in patient-reported outcome measures (PROMs) and radiographic spinopelvic parameters were found, of which 20 were eligible for meta-regression analysis. Of these, 2 correlations were significant: pelvic tilt (PT) versus Oswestry Disability Index (ODI) ($p = 0.009$) and PT versus visual analog scale (VAS) pain ($p = 0.008$).

Conclusions: On the basis of the current literature, lower PT was significantly correlated with improved ODI and VAS pain in patients with sagittal malalignment caused by lumbar degenerative disorders that were treated with surgical correction of the sagittal balance.

Background

The curvatures of the human spine are unique compared with other species As a result of evolution from quadrupedalism to bipedalism, only humans developed sagittal curvatures to maintain the head straight above the pelvis in a bipedal position. These curves were first described by Hippocrates (460-370 BCE) as "ithiscolios," indicating that the spine is curved in the sagittal plane but straight in the coronal plane[1]. In cases of spinal pathology affecting the spinal curvatures as a whole, such as severe idiopathic adolescent scoliosis or ankylosing spondylitis, surgical correction of the spine is crucial to prevent loss of pulmonary function or a forward- stooped posture later in life. The spinal curvatures can also be influenced by segmental or short-trajectory spinal pathology such as degenerative disc disease, vertebral fracture, infection, and malignancy. Because of local deformity and compensatory postural changes, spinal equilibrium (referred to below as spinal sagittal alignment) can be affected. For many years, spinal surgeons were mainly focused on local treatment of spinal pathology without regard to overall spinal alignment. Current treatment guidelines for lumbar degenerative disorders, affecting up to 60% of the aging adult population[2], are focusing on patient-reported outcome measures (PROMs), which are assessed by pain, disability, and health-related quality-of-life measurements. However, these PROMs are influenced by the balance of the entire spine. With the increasing awareness of the importance of spinopelvic parameters for proper functioning of the spinal column, many spinal surgeons have adopted the assumption that restoration of this alignment would lead to a better clinical outcome[3-11]. However, there is little direct evidence that surgical restoration of spinal sagittal alignment improves patient-reported outcomes. The aim of this study was to assess the correlation between patient-reported outcomes and achieved sagittal alignment of the spine in patients with lumbar degenerative disorders.

Materials and Methods

The methodology of this meta-analysis and systematic review was designed according to common guidelines for systematic reviews such as those given in the Cochrane Handbook. Reporting was structured according to the PRISMA (Preferred Reporting

Items for Systematic reviews and Meta-Analyses) statement[12]. The primary aims of this study were (1) to assess the correlation between patient-reported outcomes and actual obtained spinal sagittal alignment in adult patients with lumbar degenerative disorders who underwent surgical treatment, and (2) to give an overview of the measurements that are used to determine sagittal alignment of the spine.

Search Strategy

The PubMed, Cochrane, Web of Science, and Embase databases were searched on November 1, 2018, and reference lists of included studies were checked for additional studies. The search strategy for PubMed is reported in Table 1, and the search strategy for the other databases was adapted to the specific database requirements. The results of the search were exported to a database (RefWorks version 2.0; ProQuest), and all duplicate entries were identified and removed.

Table 1. Search Strategy in PubMed

Dimension	Search Strings
Sagittal	(((("sagittal balance"[tiab] OR "sagittal imbalance"[tiab] OR "sagittal alignment"[tiab] OR "sagittal malalignment"[tiab] OR alignment "C7 plumb line"[tiab] OR "sagittal vertical axis"[tiab] OR "pelvic tilt"[tiab] OR "sacral slope"[tiab] OR "sacral tilt"[tiab] OR "pelvic incidence"[tiab] OR "spinopelvic parameters"[tiab] OR "pelvic parameters"[tiab]))))
Outcome	((HR-PRO[tiab] OR HRQL[tiab] OR HRQoL[tiab] OR QL[tiab] OR QoL[tiab] OR quality of life[tw] OR life quality[tw] OR health index*[tiab] OR health indices[tiab] OR health profile*[tiab] OR health status[tw] OR ((patient[tiab] OR self[tiab] OR child [tiab] OR parent[tiab] OR carer[tiab] OR proxy[tiab]) AND ((report[tiab] OR reported[tiab] OR reporting[tiab]) OR (rated[tiab] OR rating[tiab] OR ratings[tiab]) OR based[tiab] OR (assessed[tiab] OR assessment[tiab] OR assessments[tiab])))) OR ((disability[tiab] OR function[tiab] OR functional[tiab] OR functions[tiab] OR subjective[tiab] OR utility[tiab] OR utilities[tiab] OR wellbeing[tiab] OR wellbeing[tiab]) AND (index[tiab] OR indices[tiab] OR instrument[tiab] OR instruments[tiab] OR measure[tiab] OR measures[tiab] OR questionnaire[tiab] OR questionnaires[tiab] OR profile[tiab] OR profiles[tiab] OR scale [tiab] OR scales[tiab] OR score[tiab] OR scores[tiab] OR status[tiab] OR survey[tiab] OR surveys[tiab])))) OR PROM[tiab] OR PROMs[tiab])

Study Selection

Selection was performed by 2 reviewers independently, with discrepancies resolved by a consensus meeting including a referee if necessary. Studies were selected on the basis of the following criteria. (1) Studies: both prospective and retrospective cohort studies were eligible. No minimum follow-up was required. (2) Types of patients:

studies on surgically treated patients with lumbar degenerative disorders (degenerative disc disease, degenerative lumbar scoliosis, degenerative spondylolisthesis) and adult spinal deformity (ASD) were included. (3) Types of outcome measurements: preoperative and postoperative clinical outcomes and radiographic measurements were required. The primary outcomes that were included were (1) spinopelvic radiographic parameters (Fig. 1) and (2) PROMs. The PROMs included, but were not limited to, the Oswestry Disability Index (ODI)[13], Japanese Orthopaedic Association (JOA) score[14], Scoliosis Research Society (SRS) score[15], Short Form (SF) Health Survey[16], Roland-Morris Disability Questionnaire, (RMDQ)[17], EuroQol-5 Dimensions (EQ-5D) health questionnaire[18], and visual analog scale (VAS) for pain[19]. If a reference could not be excluded on the basis of the title and abstract, the full-text article was retrieved.

Quality Assessment

Risk of bias was assessed with the Newcastle-Ottawa quality assessment scale[20]. Risk of bias was considered low if studies met at least 50% of the quality items.

Data Extraction

Selected data were imported into Excel 2020 (Microsoft) for further processing. Data extracted were the first author, year of publication, sample size, design (prospective or retrospective), follow-up period, diagnosis, intervention, and preoperative and postoperative radiographic measures and PROMs, including the corresponding standard deviations. For articles with missing data, the corresponding authors were contacted; 3 attempts were made in order to collect as much information as possible.

Analysis

A synthesis was performed on the outcome (correlation) level, integrating the results from different studies reporting identical types of correlations. A pooled correlation coefficient was calculated, indicating the heterogeneity. In this synthesis, the quality, the consistency, and the precision of the evidence were taken into account together with the probability of publication bias and indirectness of evidence as well as the quality of evidence[21]. Random-effects meta-analysis was conducted using the metanpackage in Stata (StataCorp)[22]. Pooling was performed after Fisher z transformation of the correlation coefficient; the standard erros was calculates as 1/ √n-3. Back-transformed correlations and their confidence intervals are also reported.

Figs. 1-A through 1-J. Overview of spinopelvic radiographic parameters. Fig. 1-A Sacral vertical axis (SVA)/C1 plumb line (C1pl): the distance between the plumb line from the vertebral body center of C1 and the posterosuperior corner of the superior end plate of S1. Fig. 1-B T1 pelvic angle (TPA): the angle between the line connecting the vertebral body center of T1 to the midpoint between the femoral heads and the line connecting the center of the superior end plate of S1 to the midpoint between the femoral heads. Fig. 1-C T1-spinopelvic inclination (T1-SPi): the angle between the line connecting the vertebral body center of T1 to the midpoint between the femoral heads and a vertical line. Fig. 1-D T9-spinopelvic inclination (T9-SPi): the angle between the line connecting the vertebral body center of T9 to the midpoint between the femoral heads and a vertical line. Fig. 1-E Lumbofemoral angle (LFA): the angle between the line connecting the center of the superior end plate of S1 to the midpoint between the femoral heads and the line connecting the center of the superior end plate of L1 to the midpoint between the femoral heads. Fig. 1-F Global sagittal axis (GSA): the angle between the line connecting the midpoint between the 2 distal femoral condyles to the vertebral body center of C1 and the line connecting the midpoint between the 2 distal femoral condyles to the posterosuperior corner of the superior end plate of S1. Fig. 1-G Lumbar lordosis (LL): the angle between the superior end plate of L1 and the superior end plate of S1. Fig. 1-H Sacral slope (SS): the angle between the superior end plate of S1 and a horizontal line. Fig. 1-I Pelvic tilt (PT): the angle between the line connecting the center of the superior end plate of S1 to the midpoint between the femoral heads and a vertical line. Fig. 1-J Pelvic incidence (PI): the angle between the line perpendicular to the endplate of S1 and the line connecting the center of the superior end plate of S1 to the midpoint between the femoral heads.

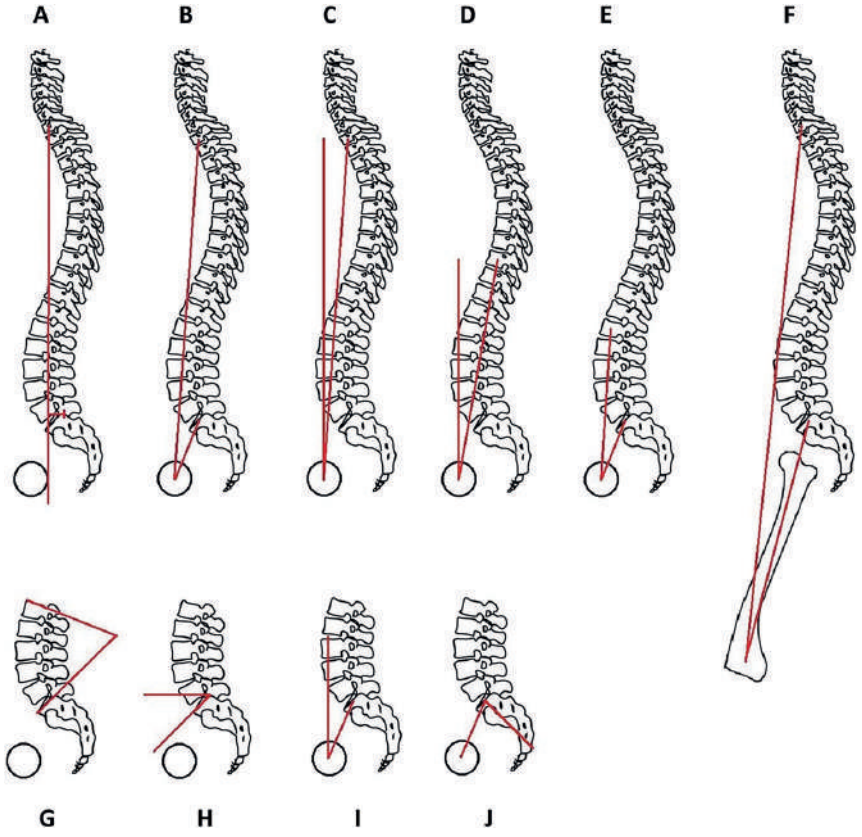
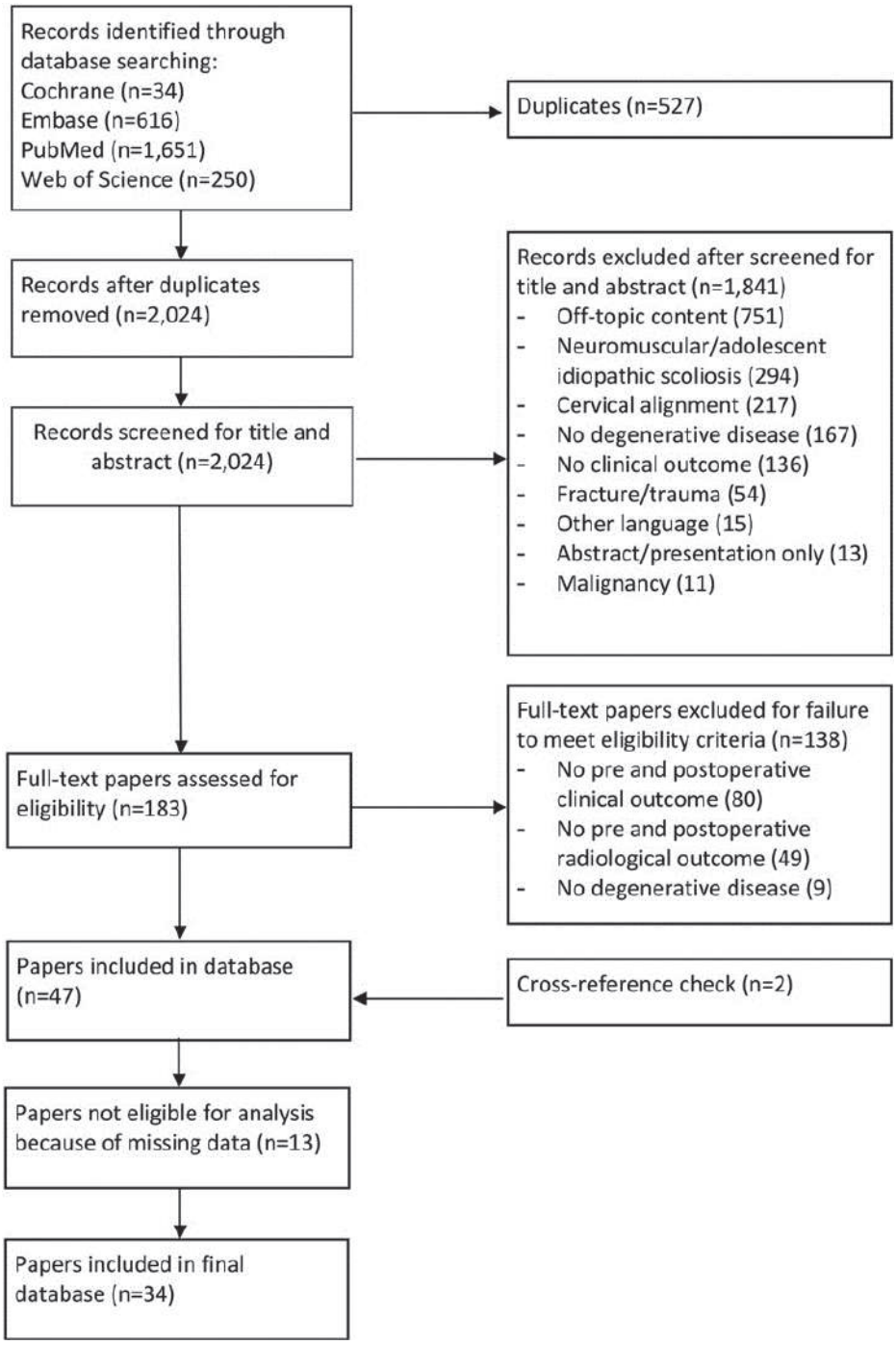


Fig 2: flowdiagram for the search strategy



Results

Search Results

The flowchart for the search and selection process is shown in Figure 2. Of 2,024 articles in the original search, 1,979 were excluded. Checking of the reference lists yielded 2 additional relevant articles, which were included. In total, 47 articles were selected for further review, and 13 of these were excluded because of missing data. The remaining 34 articles[5,9,23-54], describing 973 patients, were included in this meta-analysis. All studies were either retrospective or prospective cohort studies; the average Newcastle-Ottawa quality assessment scale was 77%, and 29% were considered at low risk of bias. The mean follow-up was 28.4 months (range, 6 to 75.6 months). Tables 2, 3, and 4 report the characteristics of the included studies, the number of correlations, and the quality of evidence (as assessed by the Newcastle-Ottawa Scale), respectively.

Table 2. Characteristics of Included Studies*

Study	Year	Sample Size	Design	Follow-up *(mo)*	Diagnosis	Intervention	Radiographic Outcome	PROM
Alimi[23]	2014	90	Retrospective	12.6	Lumbar DDD	XLIF	PI2LL	ODI, VAS
Aoki[24]	2015	52	Prospective	16.9	Lumbar DDD	Short-segment TLIF	PI2LL	ODI, VAS
Ayhan[25]	2016	121	Prospective	12	Lumbar DDD	SPO/PSO	SVA, PT, LL	ODI, SF-36, SRS-22
Blondel[26]	2012	76	Retrospective	24	ASD	Spinal fusion	SVA	ODI, SRS-30, SF-12
Bourghli[27]	2017	164	Retrospective	24	ASD	Posterior fusion	SVA, PI2LL, PT, LL	ODI, SF-36, SRS-22
Chang[28]	2017	55	Retrospective	55	Lumbar DDD	PSO	SVA, PT, LL	ODI, VAS
Cho[29]	2008	50	Retrospective	51.6	Degenerative lumbar scoliosis	Posterior fusion	SVA, LL	ODI
Cho[30]	2017	88	Retrospective	24	Lumbar DDD	24	SVA, PT, LL	ODI, EQ-5D, VAS
Cogniet[31]	2016	63	Prospective	23.5	Degenerative lumbar scoliosis	PSO	SVA, PT, LL. SS	ODI, SF-36, VAS
Demirkiran[32]	2016	8	Retrospective	18.4	ASD	ACR	SVA, PT, LL	ODI, EQ-5D
Du33	2016	43	Retrospective	27.6	ASD	Posterior fusion	SVA, PT, LL	ODI
Endo[34]	2010	61	Retrospective	6	Lumbar disc herniation	Herniectomy	SVA, LL	JOA
Farrokhi[35]	2018	88	Prospective	24	Degenerative lumbar stenosis	PLIF	SVA, PT, LL	ODI, VAS
Fujii[36]	2015	88	Retrospective	12.8	Degenerative lumbar stenosis	Lumbardecompression	SVA, PI2LL, PT, LL	VAS
Hikata[37]	2015	109	Retrospective	30	Degenerative lumbar stenosis	Lumbar decompression	SVA, PT, LL	RMDQ, JOA, VAS
Hosseini[38]	2017	39	Retrospective	13.3	ASD	ALIF	SVA, PI2LL, PT, LL, T1SPi	ODI, SRS-22, VAS
Hyun[39]	2010	13	Retrospective	36	Degenerative sagittal imbalance	PSO	SVA, LL	ODI
Kawakami[5]	2002	47	Retrospective	?	Degenerative lumbar spondylolisthesis	Posterolateral spinal fusion	LL	JOA
Kim[40]	2011	18	Retrospective	24	Degenerative lumbar spondylolisthesis	Posterior interbody fusion	SVA, PT, LL, SS	ODI, VAS
Kim[41]	2016	32	Retrospective	75.6	ASD	Posterior fusion	SVA, PI2LL, PT, LL	ODI, SRS-22
Lazennec[42]	2014	46	Prospective	24	Lumbar DDD	Total disc replacement	PT, LL	ODI, VAS
Lee[43]	2017	70	Retrospective	72	Lumbar DDD	TLIF	SVA, PT, LL	ODI, VAS
Louie[44]	2018	25	Retrospective	34.8	Lumbar DDD	LLIF	PI2LL, LL	ODI, VAS
Marchi[45]	2012	8	Retrospective	24	Lumbar DDD	ALIF	SVA, PT, LL	ODI, VAS

Table 2. Characteristics of Included Studies* (continued)

Study	Year	Sample Size	Design	Follow-up *(mo)*	Diagnosis	Intervention	Radiographic Outcome	PROM
Massie[46]	2018	39	Retrospective	18	Degenerative spondylolisthesis	TLIF	SVA, PI2LL, PT, LL	ODI, VAS
Park[47]	2015	105	Retrospective	31.3	ASD	Posterior fusion	SVA, PI2LL, PT, LL	ODI, VAS
Rose[48]	2009	40	Retrospective	24	ASD	PSO	SVA, LL	ODI, SRS-22
Schwab[49]	2013	177	Prospective	12	ASD	Posterior fusion	SVA, PI2LL, PT	ODI, SRS, SF-36
Smith[9]	2015	227	Retrospective	24	ASD	Deformity surgery	SVA, PI2LL, PT, LL	ODI, SRS-22, SF-36
Sun[50]	2017	74	Retrospective	38.4	ASD	Posterior fusion	PI2LL, LL	ODI, JOA, VAS
Than[51]	2017	76	Retrospective	33.5	ASD	Posterior fusion	SVA, PI2LL, PT, LL	ODI, VAS
Yang[52]	2015	56	Retrospective	?	Degenerative scoliosis	Posterior fusion	LL	ODI, VAS
Yasuda[53]	2017	56	Prospective	?	ASD	Posterior fusion	SVA, PI2LL, PT, LL	ODI
Zou[54]	2014	68	Retrospective	7.9	Degenerative scoliosis	Posterior instrumentation	SVA, PT, LL, SS	ODI

*DDD = degenerative disc disease, XLIF = extreme lateral interbody fusion, TLIF= transforaminal lumbar interbody fusion, SPO = Smith-Petersen osteotomy, PSO = pedicle subtraction osteotomy, ACR = anterior column release, ASD = adult spinal deformity, PLIF = posterior lumbar interbody fusion, and ALIF = anterior lumbar interbody fusion.

Table 3. Number of Manuscripts Reporting Correlations Between PROMs and Radiographic Outcomes

Radiographic Outcome	PROM	No.
SVA	ODI	23
	JOA	3
	SRS	13
	SF-12	1
	SF-36	8
	RMDQ	1
	EQ-5D	1
	VAS	8
PI2LL	ODI	15
	JOA	1
	SRS-22	8
	SF-36	4
	EQ-5D	1
	VAS	6
PT	ODI	15
	JOA	1
	SRS-22	9
	SF-12	4
	SF-36	3
	EQ-5D	1
	VAS	4
LL	ODI	11
	JOA	2
	SRS-22	4
	SF-12	4
	SF-36	1
	VAS	4
TPA	ODI	5
	SRS-22	4
	SF-12	1
	SF-36	2
	EQ-5D	1
	VAS	1
T1SPi	ODI	5
	SRS-22	3
	SF-12	2
	SF-36	1
	VAS	1

Table 3. Number of Manuscripts Reporting Correlations Between PROMs and Radiographic Outcomes (continued)

Radiographic Outcome	PROM	No.
SS	ODI	7
	SRS	2
	SF-12	2
	SF-36	1
	VAS	3
T9SPi	ODI	3
	SRS	1
	SF-12	1
GSA*	ODI	1
	SRS-22	1
	EQ-5D	1
	VAS	1
LFA	ODI	1
	SF-36	1
	VAS	1

*GSA = global sagittal axis.

Table 4. Quality of Evidence as Assessed by the Newcastle-Ottowa Scale (NOS)

	Selection	Comparability	Outcome	Total *(%)*
Alimi[23]	3	2	3	89
Aoki[24]	3	2	2	78
Ayhan[25]	3	2	3	89
Blondel[26]	4	2	3	100
Bourghli[27]	4	2	2	89
Chang[28]	3	1	4	89
Cho (2008)[29]	2	2	2	67
Cho (2017)[30]	4	2	2	89
Cogniet[31]	4	1	3	89
Demirkiran[32]	3	2	2	78
Du33	3	2	2	78
Endo[34]	3	1	0	44
Farrokhi[35]	2	1	3	67
Fujii[36]	3	2	2	78
Hikata[37]	3	2	1	67
Hosseini[38]	3	2	1	67
Hyun[39]	4	1	2	78

Table 4. Quality of Evidence as Assessed by the Newcastle-Ottowa Scale (NOS) (continued)

	Selection	Comparability	Outcome	Total *(%)*
Kawakami[5]	4	1	2	78
Kim (2011)[40]	4	1	3	89
Kim (2016)[41]	3	1	3	78
Lazennec[42]	4	1	2	78
Lee[43]	4	1	3	89
Louie[44]	4	1	2	78
Marchi[45]	4	1	2	78
Massie[46]	4	1	3	89
Park[47]	2	1	3	67
Rose[48]	4	1	0	56
Schwab[49]	4	1	0	56
Smith[9]	3	1	3	78
Sun[50]	2	1	3	67
Than[51]	3	1	2	67
Yang[52]	4	1	2	78
Yasuda[53]	4	1	2	78
Zou[54]	3	2	2	78

Outcomes

The primary aim of this study was to assess the correlation between PROMs and actual obtained spinal sagittal alignment in adult patients with lumbar degenerative disorders who underwent surgical treatment. Nine different PROMs (ODI, SF-12 or 36, SRS-22 or 30, EQ-5D, RMDQ, JOA, and VAS) were used as the clinical outcome in the included studies. The ODI was used in 88% (all but 4[5,34,36,37]) of the articles. The ranges and minimal clinically important differences (MCIDs) were obtained from the literature[14,55-58]. Improvement exceeding the MCID was found for most (89%) of the studies; for the ODI, 97% (all but 1[46]) of the studies reported improvement exceeding the MCID.

A meta-regression analysis was performed to assess the correlations. A total of 54 relations between preoperative-to-postoperative improvement in PROMs and radiographic spinopelvic parameters were found in the included articles. Despite several attempts to obtain missing data from the corresponding authors, this yielded no additional useful data. The data sets of 13 of the manuscripts were not eligible

for our regression analysis because they were incomplete. Furthermore, several relationships between certain PROMs (SRS, SRS-30, SF-12, RMDQ, and EQ-5D) and any radiographic outcome measure were reported only once in the included articles and could therefore not undergo metaregression analysis. In total, 20 relationships were available for analysis (Table 5). Of these, 2 had significant correlations: lower postoperative pelvic tilt (PT) was correlated with a lower ODI (p = 0.009), and lower PT was correlated with less pain (p = 0.008).

Table 5. Meta-Regression Analysis*

	EQ-5D	JOA	ODI	RMDQ	SF-12	SF-36	SRS-22	SRS-30	VAS
LL	†	NS (21.592 to 0.832)	NS (20.172 to 0.365)	‡	†	NS (20.662 to 0.662)	NS (20.237 to 0.196)	†	NS (20.335 to 0.500)
PI–LL	†	‡	NS (20.541 to 0.628)	†	†	NS (29.544 to 8.777)	NS (20.757 to 0.639)	†	NS (0.669 to 1.419)
PT	†	‡	0.009 (0.321 to 1.986)	‡	†	NS (21.963 to 2.109)	0.131 (20.369 to 0.098)	†	0.008 (0.455 to 2.586)
SS	†	†	NS (22.023 to 3.002)	†	†	†	‡	†	NS (21.230 to 2.742)
SVA	†	NS (20.389 to 0.556)	NS (20.132 to 0.110)	‡	‡	NS (20.132 to 0.236)	NS (20.040 to 0.051)	‡	0.068 (20.020 to 0.484)

*The values are given as the p value, with the 95% confidence interval of the regression coefficient in parentheses. NS = not significant (p > 0.20). †No analysis possible;
≤1 observation. ‡No analysis possible; a single study.

The secondary aim of this study was to assess the radiographic measurements that are used to measure sagittal alignment of the spine. The sagittal vertical axis (SVA) was the most frequently used spinopelvic radiographic outcome (in 79% [27] of the studies). This parameter is used interchangeably with the C7 plumb line. In total, data for 5 radiographic parameters (lumbar lordosis [LL], pelvic incidence [PI]–LL mismatch, PT, sacral slope [SS], and SVA) were eligible for the regression analysis, and the only significant relationships were for PT versus health- related quality of life and pain. The global angular measurements such as spinopelvic angle and T1 pelvic angle (TPA) could not be analyzed in the meta-regression because these were used in only 1 study.

Discussion

This systematic review and meta- analysis found low-quality evidence that surgical correction of spinopelvic parameters may lead to a better clinical outcome. However, since the studies were not controlled trials, serious bias such as regression to the mean, patient selection, and placebo effects makes the findings difficult to value. In addition to the low-quality evidence, the articles could demonstrate only associations, and not causality, since they were not randomized trials. Unfortunately, all of the included studies were observational, and in some of them the correction of sagittal malalignment was not the primary aim but rather a side-effect of the surgery. This means that the correlation could be confounded by other conditions that were treated, such as painful spondylolisthesis. On the other hand, the results of the regression analysis indicated a correlation between lower PT and decreased disability and pain (ODI and VAS), suggesting a causal relationship. This meta-analysis therefore constitutes the current best, although still not strong, evidence of a correlation between improved spino-pelvic parameters after surgical correction and improved clinical outcome. However, even with our extensive search and data analysis, only a minor ity of the correlations between PROMs and radiographic parameters were found to be significant.

Many parameters have been used to describe the sagittal alignment of the spine on radiographic assessments, and new parameters are still being added. Although it is cumbersome because of its need for calibration[59], the SVA is the most commonly used parameter for measuring sagittal alignment, both in this study (79% of the included articles) and in the recent literature. Newer parameters such as the TPA, T1/T9 spinopelvic inclination (T1-SPi/T9- SPi), and lumbofemoral angle (LFA) have been proposed to obviate the need for calibration by angular measurements[60-63]. Even more recently, the C2 incidence (C2I) angle and parameters using the midline of the skull as a reference point to analyze global spinal alignment have been described[64]. However, none of the studies that used these newer parameters could be included in the regression analysis due to missing data, and we were therefore unable to assess their correlation with PROMs.

In an earlier study by Glassman et al., an SVA of >5 mm was associated with decreased health-related quality of life[65]. More recently, there has been an increasing understanding of ageadjusted normative values for the SVA and other spinopelvic parameters. Iyer et al. studied 115 healthy volunteers and found a relatively strong correlation between increased SVA and age ($r = 0.46$, $p < 0.001$), without increased back pain and disability[11]. However, in the evaluation of spinal sagittal alignment, acknowledgment of compensating mechanisms is crucial. The reciprocal association among pelvic parameters has a key role in evaluation of these mechanisms. Because of the minimal motion that is possible in the sacroiliac joint, PI, PT, and SS can be mathematically linked by the formula PI 5 PT 1 SS[66]. Although PI increases slightly during growth, it then remains relatively constant during adulthood[67]. Pelvic retroversion (increase in PT and decrease in SS) is a compensatory mechanism that allows the patient to maintain a balanced standing posture in which other radiographic spinal parameters are within the normal range. Therefore, PT is a sensitive parameter to measure compensatory mechanisms in patients with sagittal malalignment. In this meta-analysis, PT was the only radiographic parameter that was found to be significantly correlated with a PROM: a decrease in PT was significantly related to improvements in the ODI and VAS. This is consistent with the study by Lafage et al.[7], in which an analysis of spinal sagittal alignment in nonsurgically treated patients found PT to be correlated with the SRS ($r = -0.29$) and ODI ($r = 0.30$).

Although the correlations were weak to moderate, PT is essential to assess compensatory mechanisms and is therefore still a key element in the analysis of an increasing understanding of age-adjusted normative values for the SVA and other spinopelvic parameters. The key nature of PT is even clearer in patients who are not able to achieve increased PT because of hip arthrosis and are therefore at significantly greater risk of unbalanced sagittal spinopelvic alignment ($p < 0.05$)[68].

Preoperative planning of correction involves many factors, such as age and the patient anatomy. Lafage et al.[69] found that patients ≥75 years old still had an average ODI score of 20 despite a PI2LL mismatch of 8.3°, whereas younger patients (35 to 44 years old) with the same ODI score had a PI2LL mismatch of 22.7°. On the other hand, correction of LL to within 69° of PI is suggested by Schwab et al.[49] as a rule of thumb for patients with flat-back deformity due to degenerative disorders. In an attempt to better assess the spino-pelvic parameters, including the proportion of the LL derived from L4-S1, the Global Alignment

and Proportion (GAP) score was developed to predict adequate surgical restoration. This allows the identification of patient-specific surgical goals and may result in better outcomes and prevent mechanical complications due to overcorrection or undercorrection[70].

Limitations

The greatest limitation of our study is the quality of the included papers and the lack of quantification of data. Many articles had to be excluded because clinical and/or radiographic outcome measurements were not available, even after multiple requests to the corresponding authors. Publication bias should also be considered, although the comprehensive search strategy in the present study tried to limit this.

Implications for Further Research

To conduct a randomized controlled trial comparing surgery aimed or not aimed at restoration of sagittal balance would be unethical. Prospective studies are therefore more feasible and may be as accurate as randomized controlled trials[71]. Authors should be encouraged to publish prospective cohort studies that compare clinical and radiographic outcome parameters during follow-up of surgical cases, and a supplementary document with all data should be made available. Angular measurements are less prone to bias than measurements that measure a distance between two points. Greater use of the newer radiographic parameters may enable better assessment of their relationships with PROMs. Also, standard outcome measures should be used to report clinical outcomes, and correlations of these outcomes with radiographic parameters should be assessed and reported.

Conclusions

This systematic review of the literature and meta-analysis found significant correlations between decreased PT and decreased ODI and VAS in patients with lumbar degenerative disorders that were treated surgically. On the basis of the currently available literature, this review provides the best, yet still low-quality, evidence for the effect of restoration of the alignment during surgery. To improve the quality of research, standard clinical outcome parameters should be used in future studies so that correlation analysis can be performed.

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ARE THE ROLAND MORRIS DISABILITY QUESTIONNAIRE AND THE OSWESTRY DISABILITY INDEX INTERCHANGEABLE IN PATIENTS WITH DEGENERATIVE LUMBAR DISC DISORDERS?

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ABSTRACT

Background: Low back pain is a common health problem and there are several treatment options. For optimizing clinical decision making, evaluation of treatments and research purposes it is important that health care professionals are able to evaluate the functional status of patients. Patient reported outcome measures (PROMs) are widely accepted and recommended. The Roland Morris Disability Questionnaire (RMDQ) and the Oswestry Disability Index (ODI) are the two mainly used condition-specific patient reported outcomes. Concerns regarding the content and structural validity and also the different scoring systems of these outcome measures makes comparison of treatment results difficult.

Objective: Aim of this study was to determine if the RMDQ and ODI could be used exchangeable by assessing the correlation and comparing different measurement properties between the questionnaires.

Methods: Clinical data from patients who participated in a multicenter RCT with 2 year follow-up after lumbar spinal fusion were used. Outcome measures were the RMDQ, ODI, Short Form 36 – Health Survey (SF-36), leg pain and back pain measured on a 0 - 100 mm visual analogue scale (VAS). Cronbach's alpha coefficients, Spearman Correlation Coefficients, multiple regression analysis and Bland Altman plots were calculated.

Results: 376 completed questionnaires filled out by 87 patients were used. The ODI and RMDQ had both a good level of internal consistency. There was a very strong correlation between the RMDQ and the ODI ($r=0.87$; $p<0.001$), and between the VAS and both the ODI and RMDQ. However, the Bland Altman plot indicated bad agreement between the ODI and RMDQ.

Conclusions: the RMDQ and ODI cannot be used interchangeably, nor is there a possibility of converting the score from one questionnaire to the other. However, leg pain and back pain seemed to be predictors for both the ODI and the RMDQ.

Introduction

Low back pain is a common health problem. Lifetime prevalence is estimated between 60% and 90% and it is a leading global cause of years lived with disability (YLDs) [1]. Low back pain is a major contributor to global health costs due to activity limitation and secondary costs due to work absenteeism and work cessation [2]. There are several treatment options for low back pain depending on the underlying cause including both surgical and non-surgical options. For optimizing clinical decision making, evaluation of treatments and research purposes it is important that health care professionals are able to evaluate the functional status of patients. In addition to objective information obtained from clinical tests, subjective patient reported outcome measures (PROMs) are widely accepted and even recommended as important outcome tools [3].

To evaluate the functional status in patients with back pain, the Roland Morris Disability Questionnaire (RMDQ) and the Oswestry Disability Index (ODI) are the two mainly used condition-specific patients reported outcome measures [4]. Both instruments are focused on pain and aspects of daily living and are therefore assumed to measure the same constructs [5]. A recent systematic review showed that there are no strong reasons to prefer the RMDQ or the ODI in patients with nonspecific low back pain regarding measurement properties [6].

As a result, both outcome measures are used arbitrary depending on the preferences of the clinician or researcher. For example, the North American Spine Society (NASS) have recommended the use of the ODI to assess the functional outcome following spinal fusion [7]. However a recently published study showed the RMDQ is still widely used in practice [8]. This lack of consensus and the different scoring systems of these outcome measures makes comparison of treatment results more difficult. The difference in scaling of the outcome measurements also results in differences in Standard error of measurement (SEM) and the Minimal detectable change (MDC). Furthermore, recently concerns were raised regarding the content and structural validity of the RMDQ and the ODI; suggesting further research to fill existing gaps on content and structural validity [9].

The main research question of this study was if the RMDQ and ODI measure the same construct and can thus both be used in evaluation of treatments and research purposes. As a subsidiary question it was studied if patient characteristics (age, gender, Body Mass Index (BMI), smoking, VAS leg pain and VAS back pain) were predictive for the ODI and RMDQ scores.

Materials & Methods

Patient sample and data gathering

Clinical data were gathered from patients who participated in a double blinded randomized controlled trial [10]. A summary of the study protocol is available on the clinicaltrails.gov website (Identifier NCT01557829). In short, patients (18 to 75 years old) presenting with a history of chronic low back pain with or without leg pain that did not respond to conservative treatment, and who had lumbar degenerative disc disorders (Pfirrmann Grade III or higher) and/or spondylolisthesis of Grade I or II, confirmed by MRI, received a transforaminal lumbar interbody fusion with an interbody cage. Main exclusion criteria were osteoporosis, prior failed fusion at the same level, degenerative scoliosis, more than two symptomatic levels that needed fusion and active cancer or infection. We refer to the published protocol for the detailed inclusion and exclusion criteria [10]. Clinical assessments were performed preoperative and 3, 6, 12 and 24 months postoperatively. Outcome measures were the RMDQ, ODI, Short Form 36 – Health Survey (SF-36), leg pain and back pain measured on a 0-100 mm visual analogue scale (VAS). A medical ethics committee approved the trial. Informed consent was obtained from all participating patients.

Outcome measures

Roland Morris Disability Questionnaire (RMDQ)

The RMDQ is a condition-specific (back pain) self-reported instrument [11]. The validated Dutch version of the RMDQ (version 1) was used [12]. The questionnaire is composed of 24 statements covering a range of aspects of daily living. The maximum score is 24 points (one point per statement) and represents maximum disability. Clinical improvement is shown if the RMDQ score is reduces by 30% from baseline [13].

Oswestry Disability Index (ODI)

The ODI provides a self-assessed functional disability score for patients with low back pain [14]. For this study the Dutch ODI version 2.1a was used [5]. The questionnaire is divided into ten sections: one to assess pain and nine to assess limitations of various activities in daily living. Each section is scored on a 0 – 5 scale, 5 representing the greatest disability. The scores of each section are added up, multiplied by 2 and expressed as a percentage. The maximum score is 100% and expresses maximum disability. For interpretation the ODI is subdivided into five categories: 1) 0 – 20 %, representing minimal disability meaning; 2) 21 – 40 %, representing moderate disability; 3) 41%-60%, representing severe disability; 4) 61%-80% representing crippled patients; 5) 81%-100%, representing bedbound patients or patients overestimating their symptoms [14].

Short Form 36 – Health Survey (SF-36)

The SF-36 is a widely used generic health status measure [15]. In this study the validated Dutch version of the SF-36 was used [16]. The survey consists of 36 questions with standardized answers divided into eight health concepts. In this study, only the dimensions Physical functioning and Bodily pain were used. The score of each concept is the weighted sum of the answers within that particular concept. Each answer carries equal weight. The weighted sum is then transformed into a 0-100 scale where 0 represents maximum disability and 100 represents no disability.

Statistical analysis

Patient characteristics and questionnaire scores are presented as mean with the standard deviation or as frequencies with percentages. At least 50 patients are needed for reliable comparing measurement properties [17]. No distinction was made between the preoperative or different postoperative measurements as determining improvement was not the goal of this study.

Cronbach's alpha coefficients (α) were calculated for determining the internal consistency and thereby the inter-relatedness of the items within the ODI and RMDQ questionnaires [17,18]. Based on literature, both questionnaires were assumed unidimensional. Internal consistency was considered poor when alpha <0.6; reasonable between 0.6-0.7 and good between 0.71-0.95. Above 0.95 there is a

strong correlation between the items, which supports summarizing the items [17]. Floor and ceiling effects were evaluated and defined as present when ≥15% of the patients achieved respectively the lowest or highest (range ±10%) possible score [17,19].

Spearman Correlation Coefficients were calculated to measure the strength and direction of association of the total scores of the ODI, RMDQ and pain questions, as well as for the comparison of single similar items of the questionnaires. The levels of correlation were defined as very weak (0.0-0.19), weak (0.2-0.39), moderate (0.4-0.59), strong (0.6-0.79) and very strong (0.8-1.0) [20]. Multiple linear regression analysis (enter method) was used to assess the predictive value of patient characteristics on the ODI and RMDQ scores. Predictive variables that were taken into account were age, gender, BMI, smoking, VAS leg pain and VAS back pain.

Bland Altman plots (mean difference ± 1.96 x standard deviation of the difference) were created to analyze the agreement between the ODI and RMDQ and to check for systematic differences [21,22]. For creating the plots, the RMDQ was converted from a 0-24 scale to a 0-100 scale. In order to permit the possibility of composing a conversion module between the ODI and the RMDQ, first the ODI was divided into categories and then the categories were plotted against the RMDQ using a boxplot. For all statistical analyses SPSS was used (IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.). For all analyses, the level of significance was set at $p \leq 0.05$.

Results

In total, 376 completed questionnaires filled out by 87 patients were used: 72 measurements at baseline, 75 at 3 months, 79 at 6 months, 78 at 12 months and 72 at 24 months. The mean number of measurement per patient was 4 (range 1-5). Patients that did not complete both questionnaires at a time point were excluded from that specific time point. Patient characteristics and outcome measurements are presented in table 1.

Table 1. Patient characteristics (*N*=376)

	N (%)
Gender	
Male	118 (31.4%)
Female	258 (68.8%)
Smoking	
Yes	249 (66.2%)
No	114 (30.3%)
Unknown	13 (3.5%)
	Mean (standard deviation)
Age (years)	55.1 (10.8)
Body Mass Index (kg/m^2)	27.0 (4.6)
Number of measurements per patient	4 (1)
ODI (0-100)	28.2 (20.2)
RMDQ (0-24)	9.2 (6.5)
Leg pain (VAS 0-100)	31.3 (28.6)
Back pain (VAS 0-100)	39.0 (24.8)
SF-36 physical functioning (0-100)	60.8 (24.1)
SF-36 bodily pain (0-100)	53.6 (24.9)

In order to analyze whether the questions in the questionnaires were internally consistent, the Cronbach's alpha was used. The ODI and RMDQ had both a good level of internal consistency with respectively α=0.91 (10 items) and α=0.92 (24 items). Floor effects (best possible score) were present in the ODI (27.4%) as well as in the RMDQ (23.1%). No ceiling effects (worst possible score) were seen.

Spearman correlations

There was a very strong correlation between the RMDQ and the ODI (r=0.87; p<0.001). There were strong correlations between the two questionnaires and respectively VAS leg pain and VAS back pain (Table 2). The ODI and RMDQ showed also strong to very strong correlations with the two dimensions of the SF-36 (physical functioning and bodily pain).

Table 2. Spearman's rho correlation coefficients for comparing the different questionnaires (*N*=376)

	RMDQ	ODI
RMDQ	1.00	0.87
ODI	0.87	1.00
VAS leg pain	0.61	0.64
VAS back pain	0.75	0.68
SF-36 physical functioning	-0.83	-0.83
SF-36 bodily pain	-0.78	-0.81

* All correlations were significant at the 0.01 level (2-tailed)

Correlations between similar questions of the RMDQ and ODI were also calculated and are described in table 3. They showed a wide range and varied between weak and strong.

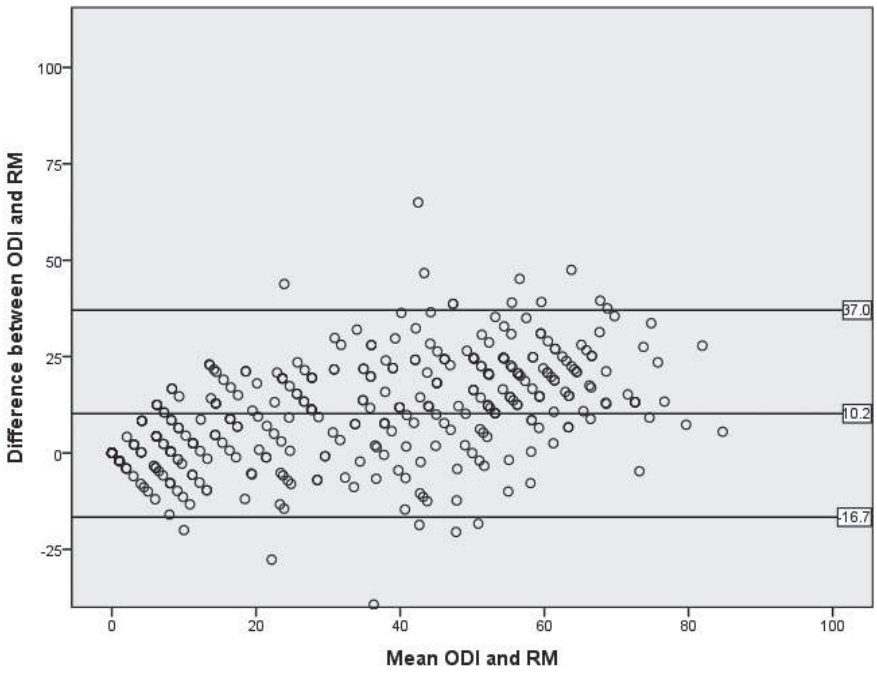
Table 3. Spearman's rho correlation coefficients for comparing separate questions of the RMDQ and ODI questionnaires.

	ODI-question	RMDQ-question	Spearman's rho (p-value)
Personal care	2	9	0.67 (p <0.001)
(washing,	2	16	0.55 (p<0.001)
dressing)	2	19	0.23 (p<0.001)
Walking	4	3	0.46 (p<0.001)
	4	17	0.55 (p<0.001)
Standing	6	10	0.33 (p<0.001)
Sleeping	7	18	0.73 (p<0.001)
Social life	9	1	0.57 (p<0.001)

Bland Altman plot

The Bland Altman plot (figure 1) indicated bad agreement between the ODI and RMDQ as the distance between the upper and lower 95% confidence interval margins were large enough to be clinically important and the variability around the mean was not constant. Furthermore, the two-sided one-sample t-test showed that the difference between the questionnaires was significantly different from zero (p<0.001) with a mean difference of 10.2 points (±13.7).

Figure 1. Bland-Alman plot with the mean and the difference between the ODI and RMDQ on respectively the x-axis and y-axis. The RMDQ was converted to a 0-100 scale. The mean difference and the 95% confidence intervals are indicated with reference lines (N=376)



Regression analysis

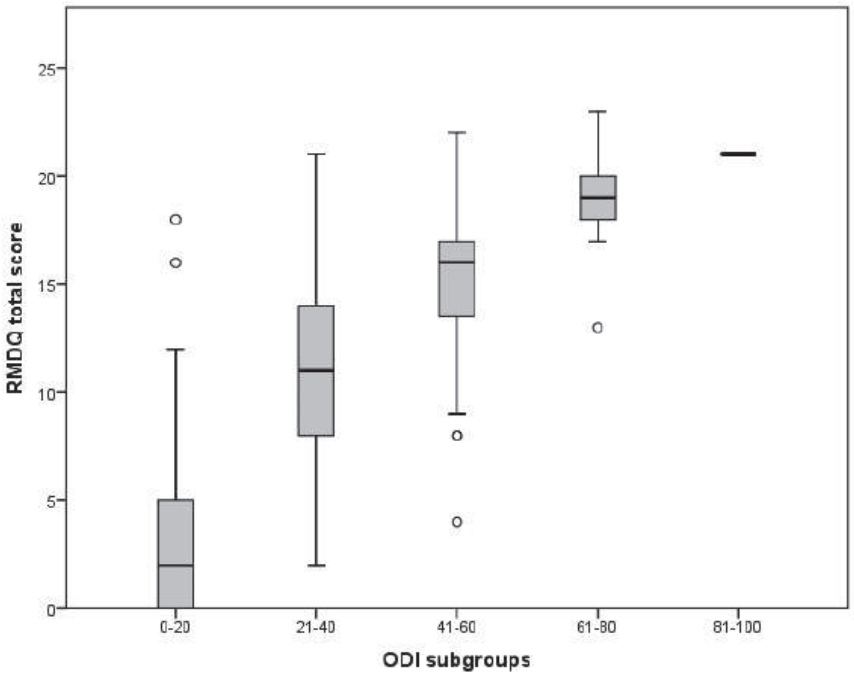
A multiple linear regression was calculated to predict the RMDQ score based on age, gender, BMI, smoking, VAS leg pain and VAS back pain. The results indicated that the predictors explained 64.2% of the variance (R^2=0.642, F(6, 345)=102.949, p<0.001). Both VAS leg pain (p<0.001) and VAS back pain (p<0.001) were significant predictors for the RMDQ (Table 4). The same was found for the ODI where the predictors explained 58.7% of the variance (R^2=0.587, F(6, 345)=81.665, p<0.001). Both VAS leg pain (p<0.001) and VAS back pain (p<0.001) were also significant predictors of the ODI.

In Figure 2, the RMDQ score of the patients is presented relative to their ODI score divided in subgroups. Only one patient fell in the worst category 81-100 of the ODI with a RMDQ score of 21. There is a clear trend visible wherein the mean RMDQ scores are ascending with the ascending ODI subgroups. However, the variability of the RMDQ scores within the subgroups were too large to define a reliable conversion equation. Therefore, it is not possible to transform the score from one questionnaire to the other.

Table 4. Multiple linear regression coefficients (n=352). The unstandardized Beta represents the slope of the line between the predictor variable and the dependent variable (RMDQ or ODI). So e.g. fo VAS back this would mean that for every one unit increase in VAS back, the outcome variable RMDQ increases by 0.158 unit (p<0.001)

	RMDQ		ODI	
	Unstandardized Beta	P-value	Unstandardized Beta	P-value
Constant	-2.333	0.238	3.264	0.623
VAS leg pain (0-100)	0.069	<0.001	0.278	<0.001
VAS back pain (0-100)	0.158	<0.001	0.405	<0.001
Age	0.016	0.451	0.085	0.226
Gender (1 = male; 2 = female)	0.335	0.482	1.102	0.491
Smoking (0 = yes; 1 = no)	-0.124	0.796	-0.355	0.826
BMI	0.074	0.113	-0.225	0.152

Fig 2. RMDQ score relative to their ODI score divided in subgroups. The mid-point line (median), lower and upper quartile are presented per subgroup. The upper and lower whiskers represent scores outside middle 50% of the scores. Outliers are indicated with a circle.



Discussion

The RMDQ and the ODI are two frequently used condition-specific patients reported outcome measures. Both are used interchangeably depending on the preferences of the clinician or researcher which makes comparison of treatment results difficult. This study tried to determine if the RMDQ and ODI could be used exchangeable. Secondly, the influence of several patient characteristics (age, gender, BMI, smoking, leg pain and back pain) on the ODI and RMDQ scores was studied.

Both the RMDQ and ODI showed good internal consistency. The individual questions of the questionnaires seem to measure one construct as previously determined and are therefore of good consistency. If the cronbach's alpha is too high (above 0.95) it could be argued that some questions are comparable to the extent that some would be redundant [17]. As the scores are respectively α=0.91 (ODI) and α=0.92 (RMDQ) no redundant questions are present. Similar cronbach alpha value on the ODI and RMDQ have been reported previously , thereby confirming the validity of our results [5,6].

Regarding floor and ceiling effect no ceiling effects were found in both the ODI and RMDQ however, floor effects were found in both. As lower values represent less disability, many of the subjects showed minimal functional disability, which indicates a limitation in distinctive character of the questionnaires.

A strong correlation of 0.87 between the RMDQ and the ODI was found similar to previous reports. A meta-analysis showed a pooled correlation of -0.66 for the RMDQ and -0.70 for the ODI with the physical functional subscale of the SF-36, which is lower than the correlations found in this study, which was -0.83 for both outcomes [6]. However, correlations between similar questions of the RMDQ and ODI varied between weak and strong (Table 3). This might be partially explained by the different answering scales. Regarding the RMDQ, each item is a statement which needs to be answered with yes or no. In contrast, the ODI uses a 6-level Likert scale, which creates a wider distribution of scores. To our knowledge, this is the first paper reporting correlations between specific RMDQ and ODI questions.

The bland Altman plots indicated bad agreement between the ODI and RMDQ. In addition, the mean difference between the questionnaires was significantly different from zero. This information contributes to the fact that the questionnaires are not interchangeable. A limitation is that the RMDQ is measured on a different scale (0 – 24) and needed to be converted to a 0-100 scale which might influence the results of the plots.

From all variables (age, gender, BMI, smoking, VAS leg pain and VAS back pain) only VAS leg pain and VAS back pain seemed to be predictors for both the ODI and the RMDQ. To our knowledge, this is the first study reporting about predictors for the ODI and RMDQ.

Lastly, the variability of the RMDQ scores within the subgroups were too large to define a reliable conversion equation. Therefore, the RMDQ and ODI cannot be used interchangeably, nor is there a possibility of converting the score from one questionnaire to the other. This cannot be explained by the sample size as the sample size is large enough. A possible reason could be that the ODI and the RMDQ are not measuring the same construct and are therefore not exchangeable [3]. Further research should attempt to clarify the use of either the ODI or the RMDQ in specific patient categories. For example, VAS pain scores from mild, moderate to severe could be used to specify patients categories.

Clinical relevance

A previous systematic review (Chiarotto, Maxwell et al. 2016) compared the measurement properties of the RMDQ with the ODI and stated that there are no strong reasons to prefer the RMDQ or the ODI in patients with nonspecific low back pain. The focus of the current study was not to assess whether one of the two instruments has better measurements properties, but to assess if they can be used exchangeable [6]. Because results showed that the ODI and RMDQ are not interchangeable, consensus on their use in clinical practice is essential to analyze treatment outcomes and provide sufficient patient counseling. To determine treatment outcomes and clinical progression, the SEM and MDC are properties that should be used.The development of national registries with standard validated PROMs could

help to gain sufficient data. For example, both the NASS and the Dutch Spine Society (DSS) have already incorporated the ODI into their registries.

Limitations

Limitations of this study include that data was collected from a study with a different goal. Secondly, more female participants than male participants and more smoking participants than non-smoking participants completed the questionnaires, which could influence the generalizability. However, this might be characteristic for this specific patient category. Thirdly, we included multiple measurements per patient at multiple time points (see above). This presents two issues. First including the same patient multiple times might introduce bias; secondly, by default these measurements are not independent. However, as determining improvement was not the goal of this study and RMDQ, ODI and SF-36 measurements were paired at the different measurement times, it was a priori hypothesized that this would not influenced the results. Lastly, the authors recognize that in order to compare two measurement properties, the properties must be calibrated on the same scale preferably. Two ways of doing so is by either development and evaluation of a crosswalk, or by using item response models. For both of these methods sufficient numbers are needed which the authors unfavorably did not have. This could be a consideration for future research.

Conclusion

The RMDQ and ODI are not interchangeable, nor is there a possibility of converting the score from one questionnaire to the other. However, VAS leg pain and VAS back pain seemed to be predictors for both the ODI and the RMDQ. Further research is needed in order to determine in which type of patient which questionnaire should be used.

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10

SUMMARY AND GENERAL DISCUSSION

Summary

The combined work in this thesis aims to improve the clinical outcome of treatment for patients with symptomatic DDD by evaluating the current practice, to report on new surgical and preventive treatment strategies, and to assess the best method for the evaluation of clinical outcome. To answer the research questions formulated in the general introduction, this thesis was structured by subdividing the research into several parts.

Part I: current practice

1. *What is the current practice regarding lumbar spinal fusion among spinal surgeons in the Netherlands?*

The demand for clinical guidelines is increasing with the upcoming importance of Evidence Based Medicine. There is a need for more uniform clinical guidelines among care givers. These should subsequently be handed to patients, insurance companies and policy makers, for whom consensus in clinical practice is essential. If we want to continue to improve the outcome for spinal surgery, it is important to understand the modern day to day practice and to understand where we came from and how we have evolved to the current level. Therefore, in **Chapter 2**, the results of an online survey, sent to all members of the Dutch Spine Society, are presented to provide an overview of the current practice. The questionnaire consisted of 30 questions focusing on indications, operative techniques, implant materials, and post-operative care after spinal fusion in patients with symptomatic degenerative lumbar disorders. Of the 79 surgeons who performed a lumbar fusion in the Netherlands, 52 surgeons responded (66%). Less invasive surgery was preferred by a minority (35%). A bilateral PLIF with two interbody cages was the most frequently performed fusion technique. The most commonly used material was a PEEK cage (44%), with local autologous bone graft considered to be the best option for cage filling (56%). There was no consensus on assessment of outcome of fusion and post-operative care. For example, to evaluate the fusion status postoperatively, CT was used significantly more often by neurosurgeons compared to orthopedic surgeons (84 % vs 31% respectively, $p<0.01$). Only 62% of surgeons used PROMS to measure the clinical outcome. VAS leg pain (52%) and VAS low back pain (48%) were most frequently used. The preferred

questionnaire for measuring physical functioning was the ODI (37%), followed by the RMDQ (14%).

2. *What is the evidence for the use of PEEK cages as preferred implant material for spinal fusion in patients with degenerative disc disorders?*

As confirmed by the questionnaire in **Chapter 2**, PEEK cages hold a dominant position as the surgeon's preferred implant material for spinal fusion surgery (1-3). To assess the evidence of good clinical outcome of PEEK cages, we performed a systematic review of all randomized controlled trials and prospective and retrospective nonrandomized comparative studies with a minimum follow-up of 6 months, and all non-comparative cohort studies with a long-term follow-up of more than 5 years. The MEDLINE, EMBASE and Cochrane Library databases were searched. Results are presented in **Chapter 3.** Because only a limited number of lumbar fusion studies were found, with large variations in indications and operative technique, only cervical fusion studies were included. Of these, a total of 223 studies were identified, of which only 10 studies could be included (two RCTs, five prospective comparative trials and three retrospective comparative trials). High fusion rates and good clinical outcome scores are reported for PEEK cages in the cervical spine. No differences were found between PEEK, titanium and carbon fiber cages. Publications of lumbar interbody fusion studies need to be promoted because differences in clinical and/or radiographic scores are more likely to be demonstrated in the lumbar spine due to a biomechanically more demanding environment. Methodologically these future publications need to be improved in order to minimize risk of bias. More standard clinical and radiographic outcome parameters should be defined and used to improve the quality of these publications.

Part II. Challenges in surgical fusion techniques: SNAP trial

3. *Are ceramic silicon nitride cages an alternative for PEEK cages to improve the outcomes for spinal fusion in patients with degenerative disc disorders?*

PEEK cages are widely used, although the evidence for its use in the literature is limited. Complications like subsidence and migration of the cage are still seen, possibly resulting from a lack of osteointegration of the cage and difficulty in

radiographic assessment. Protein absorption and cell adhesion on the smooth surface of PEEK is discouraged by the hydrophic nature of PEEK, resulting in the formation of a fibrous tissue layer around the implant (2, 4, 5). Hereby, it inhibits direct appositional bone healing, also referred to as the PEEK 'halo effect' (2, 6). Si_3N_4 was developed as an alternative material with good osteointegrative properties and was therefore expected to lower complication rates and improve fusion. Several *in vitro and in vivo* studies in small animal models have confirmed the strong mechanical and good osteointegrative qualities of Si_3N_4 (7-9). In **Chapter 4**, the fusion rate, bone volume, bone-implant contact and soft-tissue implant contact ratios were determined and measured between PEEK and Si_3N_4 using radiographic, biomechanical and histological analyses. A caprine model is used because of similarities in the axial loads, disc geometry and morphology between the intervertebral discs of humans and goats (10). Eight adult goats received a lumbar interbody fusion at two adjacent levels (always separated by one mobile disc space) using a PEEK cage and a Si_3N_4 cage. After 6 months, using micro-CT analyses, seven of eight implants in both the PEEK and Si_3N_4 group showed continuous bony bridging connecting the adjacent endplates. More bone formation was observed in the Si_3N_4 group versus the PEEK group (52.6 vs 27.9% respectively, p=0.2). There were no significant differences in the ranges of motion (flexion/extension, lateral bending and axial rotation) between the fused segments in each group. After histological analyses, appositional soft tissue dominated the implant`s interfaces with the local host bone in both the PEEK and Si_3N_4 group (93.2 and 89.2% for inside of the implants and 94.4 and 97.8% for outside of the implants respectively, p=0.6). These results suggest that Si_3N_4 implants are not inferior to PEEK and may be more effective in promoting spinal fusion. In 2008, Si_3N_4 received the CE Mark and FDA clearance for its use as an interbody cage in spinal fusion. A recently published RCT on patients undergoing anterior cervical discectomy with fusion (ACDF) reported no statistically significant differences in clinical outcome and fusion rates between PEEK and Si_3N_4 (11). However, as described in Chapter 3, differences in clinical and/or radiographic scores are more likely to be demonstrated in the lumbar spine. Therefore, in **Chapter 5**, a study protocol is presented on PEEK versus Si_3N_4 cages in patients with symptomatic lumbar DDD. The SNAP trial was designed as a non-inferiority double-blind (patient and observer) multicenter RCT with repeated measures analysis. Patients presented with chronic low back pain with or without radicular pain would undergo a single or double level

TLIF procedure using a randomly allocated PEEK or Si_3N_4 cage. Measurements were performed preoperative and at 3, 6, 12 and 24 months. The non-inferiority margin for the primary outcome of the RMDQ was 2.6 points on a scale of 24. Secondary outcomes were the SF36, ODI, VAS leg and VAS low back pain and patient and surgeon perceived Likert scores. Radiographic analyses for fusion, subsidence and segmental motion were performed by an independent radiologist using (dynamic) radiograms and CT imaging. The protocol was published to improve transparency, and provides a full overview of the methods in this study. In **Chapter 6**, the 2 year results are presented. 100 patients were included in two centers. After excluding eight patients due to protocol violations or cancellation of the surgery by the patient after inclusion, the remaining ninety two patients were randomized (*i.e.* 48 for PEEK and 44 for Si_3N_4). At 24 months, 7 patients were lost to follow-up (7.6% drop-out rate). Both treatment groups showed good clinical improvements in RMDQ scores of up to 5-8 points during follow-up. Although the PEEK group scored better outcomes at 3, 6, 12 and 24 months compared to Si_3N_4, these differences were small and not significant. Using the *a priori* selected non-inferiority margin of 2.6 points on the RMDQ scale, there was insufficient evidence to conclude that Si3N4 was non-inferior to PEEK. No significant differences were seen in SF36, ODI, VAS leg pain, VAS low back pain and Likert scores between the two groups. Based on flexion/extension analysis of angular or translation motion, no significant differences were seen between PEEK and Si_3N_4 (88% vs 82% respectively, p=0.4). Also, bony bridging measured on CT at 12 months was comparable between the two groups (p=0.13). Average operative time and blood loss were significantly higher in the Si_3N_4 group (p=0.03 and p=0.01, respectively). This can partially be explained by a higher number of 2-level procedures in the Si_3N_4 group compared to PEEK (*i.e.* 8 versus 5). Also, a higher incidence of perioperative complications and revisions seemed to be associated with the Si_3N_4 cage, although not statistically significant. In conclusion, although theoretically more favorable, the Si_3N_4 cage did not perform as expected in the clinical setting. Possibly, the increased elastic Young's modulus may play a role in this.

Part III: Challenges in therapeutic strategies and outcome measurement

4. Is temporary disc distraction a viable treatment option for degenerative disc disorders?

Parallel to the search for alternative implant materials in order to optimize osteointegration and thereby increasing fusion rates, other strategies are investigated to improve the outcome of surgical interventions in patients with symptomatic DDD. Because there are similarities between articular cartilage and the IVD, researchers investigated the option of a temporary distraction in the spine. This technique, derived from the treatment of osteoarthritic ankle and knee joints, reduces the mechanical stress on the cartilage, allows chondrocytes to initiate repair and prevents further wear and tear of the cartilage (12, 13). Restoring the functional integrity of the intervertebral disc by temporary distraction may prevent further degeneration of the involved disc and even affect adjacent segment changes that may otherwise be triggered by a fused level. This can be achieved by using a temporary pedicle-rod fixation device. Signs of tissue repair have been demonstrated in *in vivo* rabbit models (14). To assess the safety and efficiency of temporary distraction, we initiated a pilot study in a dog with clinical and radiographic signs of intervertebral disc degeneration (**Chapter 7**). Distraction was applied with a pedicle screw-rod fixation at L7-S1 in a 5-year old 31 kg male Greyhound. After 3 months, the pedicle screw-rod construct was removed in a second surgery. Follow-up was performed with lateral radiographs to measure disc height and MRI T2 mapping to evaluate intervertebral disc degeneration according to the Pfirrmann classification (15). Also, force plate analysis measured the functional status during follow-up. Disc height index in L7-S1 remained unchanged after distraction. However, assessment of the complete IVD revealed distraction of the dorsal part of the IVD and compression of the ventral area. The IVD surface area increased by 15% directly after distraction, and 20% at 3 months of distraction compared to pre-distraction. At 3 and 6 months after removal of distraction, IVD surface area decreased to values slightly higher than the initial value prior to distraction (1% and 2% respectively). Pfirrmann scores of the L7-S1 IVD remained grade II at all time-points during follow-up. Force plate analysis showed that the pelvic/thoracic propulsive force was 4% higher at 6 months after removal of distraction compared to the initial preoperative value. This pilot study

has demonstrated that a temporary distraction with a pedicle-screw rod device in a dog with degenerative disc disorders was safe, improved clinical signs using force plate analysis and retained disc height 6 months after removal of distraction. However, a secondary surgery is needed to remove the implant. It is a starting point in the treatment of low back pain due to DDD, but its clinical efficacy needs to be investigated in future studies on larger groups and longer follow-up.

5. *What is the role of sagittal alignment in the treatment of patients with degenerative disc disorders?*

Many spine surgeons are convinced that restoration of spinopelvic parameters could lead to better clinical improvement in lumbar degenerative cases (16-19). To investigate this theory, in **Chapter 8** the correlation between patients reported outcomes and achieved sagittal alignment of the spine was assessed with a systematic review and meta-analysis of the literature. The PubMed, Cochrane, Web of Science and Embase databases were searched for both prospective and retrospective cohort studies reporting on surgically treated patients with lumbar degenerative disorders. Primary outcomes were spinopelvic parameters and PROMS. Risk of bias was assessed with the Newcastle-Ottawa quality assessment scale, and was considered low if studies met at least 50% of the quality items. Of the 2024 articles in the original search, 34 articles were included describing 973 patients. 29% of the included articles were considered low risk of bias. Nine different PROMS were used to measure the clinical outcome in the included studies (ODI, SF-12 or 36, SRS-22 or 30, EQ-5D, RMDQ, JOA and VAS). ODI was used in 88% of the articles. Ten radiographic measurements were described to assess the sagittal alignment of the spine. The sacral vertical axis (SVA) was used most often (in 79% of the studies). A meta-regression analysis was performed to assess the correlations between preoperative-to-postoperative radiographic spinopelvic parameters and improvements in PROMs. Only 2 significant correlations were found: lower postoperative pelvic tilt (PT) was correlated with a lower ODI ($p=0.009$), and lower postoperative PT was correlated with less pain ($p=0.008$). This meta-analysis constitutes the current best evidence of a correlation between improved clinical outcome and improved spinopelvic parameters after surgical correction. The main limitation of this study was the low quality of included papers and lack of quantification of data, as only observational studies could

be included. To improve the quality of research, authors should be encouraged to publish prospective cohort studies reporting follow-up of surgical interventions for degenerative disorders of the lumbar spine. Also, standard clinical outcome measures and radiographic parameters should be used in future studies.

6. *Are the Roland Morris Disability Questionnaire (RMDQ) and the Oswestry Disability Index (ODI) interchangeable in patients with degenerative disc disorders after spinal fusion?*

To measure the functional status of patients after surgery for degenerative spinal disorders, the ODI and the RMDQ are the most frequently used questionnaires, as discussed in **Chapter 2** and **Chapter 8**. A systematic review stated there are no strong reasons regarding measurement properties to prefer either the RMDQ or the ODI (20). As a result, both are used arbitrarily depending on the preference of the clinician or researcher. However, comparison of treatment results between these two PROMs is difficult due to differences in content, structural validity and scoring systems. Therefore, our main research question in **Chapter 9** was whether the RMDQ and the ODI could be exchangeable by assessing the correlations and comparing different measurement properties between the questionnaires. Clinical data were gathered from patients participating in the SNAP trial. Cronbach`s alpha coefficients (α) were calculated for determining the internal consistency and thereby the inter-relatedness of the items within the RMDQ and ODI. Spearman correlation coefficients were used to measure the strength and direction of association of the total score of the ODI and RMDQ, as well as for the comparison of single similar items of the PROMs. Bland Altman plots were created to analyze the agreement between the ODI and RMDQ and to check for systematic differences. In total, 376 questionnaires filled out by 87 patients were used. Both the ODI and RMDQ had good internal consistency (α=0.91 and α=0.92 respectively). Also, strong correlations were found between the RMDQ and ODI (r=0.87, p< 0.001). Correlations between similar questions of the RMDQ and ODI varied between weak and strong. The Bland Altman plot indicated bad agreement between RMDQ and ODI. The variability of the RMDQ scores within the subgroups was too large to define a reliable conversion equation. Therefore, the questionnaires are not interchangeable. From all variables (age, gender, BMI, smoking, VAS leg pain and VAS low back pain) only VAS leg pain

and VAS low back pain were predictors for both the RMDQ and the ODI. Because the questionnaires cannot be used exchangeable, consensus on the use of either the RMDQ or ODI in clinical practice should be encouraged. We suggest using the ODI in general practice, as it possibly measures a broader construct than solely physical functioning. It displays higher cross-sectional correlations with other instruments (e.g. pain intensity, social functioning, general health, mental health) compared to the RMDQ (20). Both the North American Spine Society (NASS) and the Dutch Spine Society (DSS) have already incorporated the ODI into their registries.

General discussion

LBP is the leading cause of years lost to disability worldwide and is expected to increase even more due to aging and population growth. Therefore, it is important to improve our current treatment strategies. Only a small percentage of patient with LBP have a clearly defined pathological cause, such as a malignancy, vertebral fracture, infection, disc herniation or spinal stenosis. In the vast majority of LBP patients the etiology is poorly understood. These patients are often diagnosed with degenerative disc disease/ degenerative disc disorders (DDD). Although there are multiple population-based studies reporting strong correlations between clinical and radiographic features of LBP and DDD, the term degenerative disc disease remains controversial as there is still no widely accepted reference standard (21-26). Moreover, degeneration of the IVD is part of the natural aging of the spine and often asymptomatic. Other factors including genetic inheritance and loading history also play an important role in the process of degeneration of the IVD. Secondary changes initiated by IVD degeneration can lead to facet joint osteoarthritis, spondylolisthesis, herniated IVDs and spinal stenosis causing radiculopathy and neurogenic claudication (27-29). Although the exact mechanism of DDD is not yet fully understood, the secondary initiated symptoms offer a clearly defined pathological cause of LBP (with or without additional neurogenic pain). Therefore, in this thesis, these secondary changes were also considered being part of the diagnosis of (symptomatic) degenerative disc disorders. Consequently, given the wide variety of symptoms and (secondary) pathology, there are many challenges in the treatment of patients with symptomatic DDD. In this thesis, we have tried to order some of these challenges by subdividing them into several categories.

Part I: Current practice

If we want to continue to improve the outcome for spinal surgery, it is important to understand the modern day practice and how we got there. Therefore, in **part I**, we investigated the current practice of treatment of symptomatic DDD among spine surgeons in the Netherlands. An online survey was conducted among members of the (DSS). We believe the results are representative because almost all spine surgeons that perform instrumented spinal fusion are a member of the DSS. As discussed earlier, diagnosis of patients with DDD remains debatable. This is reflected in the clinical guideline of the NASS for the diagnosis of low back pain, updated in 2020 (30). It states there is insufficient evidence to make recommendations for or against an association between low back pain and physical examination. Also, no recommendations can be given for imaging findings correlating with the presence of low back pain on radiograph, contrast enhanced imaging, CT and MRI. Accordingly, in our survey, we found little consensus among spine surgeons in the Netherlands regarding imaging findings associated with DDD. Interestingly, respondents who would perform a spinal fusion on patients with low back pain without radicular pain used Modic changes and the Pfirrmann grade on MRI more often to diagnose DDD. Regarding spinal fusion, the majority of respondents (77%) preferred an interbody fusion technique (77%), although still 16% preferred posterolateral fusion. Interbody fusion has been reported to be superior to posterolateral fusion in terms of higher fusion rates and better restoration of sagittal balance (31, 32). The preferred choice of implant material for interbody fusion was divided; most neurosurgeons preferred a PEEK cage (78%) whereas orthopedic surgeons preferred a titanium cage most often (34%), followed by a PEEK cage (25%). In total, PEEK was the front-runner overall (44%). Conflicting evidence is found in the literature on the biomechanical qualities of PEEK. Because PEEK has a Young`s modulus much closer to that of cancellous bone compared to solid titanium (E=3.6 GPa versus E=110 GPa), this might lead to less subsidence and higher rates of fusion for PEEK cages (33). In contrast, encapsulation of PEEK cages by a fibrous tissue layer has been described in literature, thus prohibiting direct cage-bone contact (34). To examine the outcome of PEEK more closely, a systematic review of all comparative and long-term noncomparative cohort studies of PEEK cages in the treatment of DDD was performed (**Chapter 3)**. Unfortunately, only a limited number of lumbar fusion studies were found, with large variations in indications and operative technique. We therefore had to limit

our search to cervical applications of PEEK. In the cervical spine, no differences were found between PEEK, titanium and other materials. Since differences in clinical and/or radiographic scores are more likely to be demonstrated in the lumbar spine due to a biomechanically more demanding environment, publications of lumbar interbody fusion studies need to be promoted. Also, these future publications need to be improved methodologically in order to minimize risk of bias. For example, patients and researchers should be blinded for type of intervention. Also, standard PROMS to evaluate the clinical outcome should be used, next to radiographic assessment of fusion by radiograms and CT evaluated by independent radiologists.

In summary, in the current practice patients are receiving a variety of treatments for symptomatic DDD. This variety of treatments comes with its own variety of long-term outcomes. This troubles (preoperative) patient counseling, which is considered to be a major factor in achieving a good outcome of any treatment (35). Also, since different treatment strategies for patients with DDD result in different costs, transparency is asked by third-party stakeholders such as insurance companies and policy makers. This highlights the importance of clearly defined clinical guidelines and recommendations for the diagnosis and treatment of DDD. (Inter)national registries, like the Dutch Spine Surgery Registry (DSSR), the Nijmegen Decision Tool ((36), the Eurospine Spine Tango and the Swedish National Spine Register (SWESPINE), monitor the indications and the effect of treatments more closely. Analyzing and/or combining these databases will enable the scientific community to install clinical guidelines for best practice in patients with DDD.

Outcome parameters

Assessment of outcome following treatment is essential to compare the effectiveness of different treatment strategies. However, it remains a challenge to achieve consensus in outcome parameters. Assessment of clinical outcome with validated PROMS following treatment is strongly advised. However, a large percentage of spine surgeons in the Netherlands (39%) did not use any questionnaires at all in standard clinical practice (**Chapter 2**). Although there still is no consensus that a bony fusion correlates with a good clinical outcome, the ability to identify a successful fusion is considered an important element in the management of patients undergoing lumbar interbody fusion procedures (37). There is considerable controversy in the scientific literature

as to when a lumbar segment is considered radiologically fused (38, 39). It can be assessed by several radiographic techniques, including plain and dynamic radiographs, CT, MRI or bone scintigraphy. Various criteria for angular and translation motions have been proposed, next to the absence of radiolucencies at the superior or inferior surface of the implant. Static plain radiographs are relatively cheap and easy to obtain with low radiation exposure. Historically, anterior bone bridging on plain radiograph (i.e. the "sentinel sign") has been the classic indicator for a solid bony fusion. However, this does not always apply for interbody fusion cases. Whereas "sentinel signs" were present in in two cases in our caprine study , additional analysis with micro-CT imaging showed 0% bony fusion between the two endplates in these cases **(Chapter 4).** Plain radiographs are only accurate in determining bony fusion in approximately two-thirds of cases (40). CT scanning has a higher accuracy and thus, it has been recommended to use radiographs in combination with CT scanning (30, 39). Nonetheless, only half the spinal community in the Netherlands used CT scanning for follow-up **(Chapter 2)**. However, as recently confirmed by the updated NASS guideline, there is still no clear evidence that a bony fusion correlates with a good clinical outcome (30). However, a technically and/or radiographically insufficient fusion does not necessarily equates an unsuccessful clinical outcome because vertebral stability may occur before is it radiographically evident **(Chapter 4).**

Part II: Challenges in surgical fusion techniques

A solid osteointegration (anchorage of an implant achieved by direct bone-to-implant contact) might provide sufficient vertebral stability. Therefore, manufactures have been investigating material and surface modifications to create an optimal environment for direct bone-to-implant ingrowth. For example, the material has to be biological compatible without any immunological reactivity. A hydrophobic nature and smooth surface of the implant material can discourage protein absorption and cell adhesion, thereby inhibiting direct bone-to-implant contact. Also, a high Young`s elastic modules of the implant can create stress shielding and subsidence, thus promoting pseudo-arthrosis. Also of importance, the material has to be compatible with CT and MRI imaging to monitor the formation of bone. In **part II**, we investigated an alternative ceramic material ($Si_3N_{4)}$ with good osteointegrative and imaging properties. It was therefore expected to lower complication rates and improve fusion rated compared to PEEK. As a first step, three accepted methods for assessing fusion differences between

PEEK and Si_3N_4 implant groups were utilized in a caprine model: radiographic imaging (both x-ray and micro-CT), histological analyses, and biomechanical testing. The results indicated that both implant materials were effective in achieving fusion. The treated segments containing either the PEEK or the Si_3N_4 implants showed significant range-of-motion restrictions on flexion/extension, lateral bending, and axial rotation in comparison to non-treated segments. Although fusion and bone volumes of the PEEK and Si_3N_4 groups were not statistically different (*i.e.*, $p \geq 0.05$), overall the Si_3N_4 spacers showed higher average fusion percentages and greater bone volumes than the PEEK components. The histology data correlated with the imaging analyses but surprisingly also showed that soft tissue (*i.e.*, fibrous layers) dominated the interfaces between the implants and new bone growth regardless of the implant type. Possibly, the transverse screw-rod fixation did not stabilize the operated segment enough. Also, implant surface topography may have played a role in the large variability observed in fusion and in the significant amount of fibrous tissue formed around both types of cages. Studies on a number of different materials have increasingly shown that the combination of macro- (S_a or $R_a \geq 1.0$ µm), micro- (0.1 µm $\leq S_a$ or $R_a < 1.0$ µm), and nano-rough surfaces (S_a or $R_a < 0.1$ µm) are more effective in facilitating bone apposition than smooth implants (41). In this study, the average area surface roughness of both cage materials was essentially equivalent (0.6~0.8 µm). While the PEEK implants had some micro-rough features and the Si_3N_4 had nano-rough characteristics, neither implant had a broad topographical range in roughness values. Consequently, it is perhaps not unexpected that PEEK and Si_3N_4 had similar fusion and appositional bone healing characteristics. The data from **Chapter 4** indicate that the comparable appositional healing observed by both implant materials was likely influenced more by the similarity of their surface topography than their differences in chemistry. Results from **Chapter 4** also provide insight into the various imaging modalities that can be utilized to assess spinal fusion. It was found that the classic use of lateral x-ray radiography to assess fusion (*i.e.*, the "sentinel sign") overestimated the actual amount of bone bridging between the endplates in comparison to micro-CT. Furthermore, the biomechanical analysis demonstrated that adequate vertebral stability can be achieved without necessarily having continuous bone bridging between the endplates.

To compare the clinical and radiographic outcomes for Si_3N_4 cages versus PEEK cages in patients, the SNAP trial was designed **(Chapter 5, 6).** The overall results indicate

that patients treated with either cage material had comparable outcomes with respect to disability, pain, and fusion. In this study, it was hypothesized that Si_3N_4 would be non-inferior to PEEK as measured by a non-inferiority margin of 2.6 points on RMDQ scores at 12-months follow-up. Although both implant groups had improvement scores of up to 5-8 points, there was insufficient evidence to conclude that Si_3N_4 was non-inferior to PEEK. As with any non-inferiority study, this does depend directly on the non-inferiority margin of 2.6 points improvement on RMDQ that was pre-determined. Our considerations are part of the original study protocol **(Chapter 5).** However, the manufacturer of the Si_3N_4 cage did not agree with this perspective and requested us to include a post-hoc analyses in which the non-inferiority margin of 2.6 points was proven to be insufficient. They proposed a higher non-inferiority margin, thereby confirming the non-inferiority of Si_3N_4 compared to PEEK . After we declined their post-hoc analyses, they excluded us (principal investigators) to publish our view of the results of the RCT by claiming exclusive rights for the study data. Furthermore, without our consent, the manufacturer published a biased version of the 2-year results of the SNAP trial in an international spine journal, including their post-hoc analysis confirming the non-inferiority of Si_3N_4 (42). With this act, the manufacturer did not adhere to the ethical and moral standards of Evidence Based Medicine (EBM). Firstly, they acted contrary to article 36 of the Declaration of Helsinki, stating "Negative and inconclusive as well as positive results must be published or otherwise made publicly available". Also, restricting the principal investigators to publish the authentic results is deemed to be unreasonable according to the involved Medical Ethics Committee (METC) Directive on the Assessment of Clinical Trial Agreements. Moreover, the authors did not adhere to the revised International Committee of Medical Journal Editors (ICMJE) criteria. Lastly, it discloses a case of plagiarism by copying large parts of the Introduction, Methods, Results and Discussion sections combined with the figures and tables of **Chapter 6**. Methodologically, their post-hoc analysis approach is a clear case of incorrect scientific practice. Their reasoning on what constitutes a non-inferiority margin is flawed: this margin is not the minimal clinically important difference (MCID) at individual patient level, but a margin that ensures non-inferiority at population level, as well as that it is sufficiently small to be robust against constancy of effects over time (43, 44). Likewise, statistical power assessments at the design stage include that the standard deviation is not fixed but is estimated from the data. Post-hoc "power" calculations based on the observed

standard deviation can be done, but they do not constitute an assessment of power of the study (45, 46). The post-hoc analysis is fully data driven; therefore actual type 1 error (significance level) cannot be assessed and is likely inflated. The possibility to evaluate the primary results against any other non-inferiority margin than pre-defined is already perfectly possible based on our published paper **(Chapter 6)** and does not justify a separate publication. The design of the study, including the non-inferiority margin and assumptions, provided ample opportunity to challenge the margin and assumptions prior to having access to unblinded data and results. This did not happen, it only occurred at the moment the manufacturer was fully aware of complete results. We have therefore published a letter to the editor **(Appendices)** of the involved international spine journal, urging the editor to remove the publication from all publicly available platforms.

In **part II** of this thesis, we have shown that Si_3N_4 implants did not performed as expected. In the caprine study it is suggested that the topographical surface features of abiotic materials may be at least as important as their surface chemistry. Recent developments within this field include 3-D printed titanium scaffolds. With the availability of 3-D printing of titanium in a cellular structure, it became possible to manufacture a structure that provides and optimal rough and porous scaffold optimizing bone ingrowth on the surface of the implant, that closely mimics the elastic modulus of bone (47). Also, it is compatible with MRI and CT scanning. Because the material has only recently been introduced, so far only limited clinical studies are available. However, our research group is currently working on a large caprine study using these 3-D printed Ti scaffolds and results are expected to be published this year.

Part III: Challenges in therapeutic strategies and outcome measurements

In this thesis, **part III** focused on alternative challenges in treatment strategies and outcome measurements for DDD. Derived from the successful treatment of osteoarthritic ankle and knee joints, safe temporary distraction of a lumbosacral intervertebral disc was demonstrated in a pilot study in a Greyhound dog with symptomatic degenerative lumbosacral stenosis **(Chapter 7).** The dog was presented by a dog owner as a patient at the Faculty of Veterinary Medicine in Utrecht, hosting the largest academic veterinary hospital in Europe. Restoring the functional integrity of the intervertebral disc by temporary distraction may prevent further degeneration

of the involved disc and even affect adjacent segment changes that may otherwise be triggered by a fused level. However, the results of this pilot study need to be interpreted with care. Several challenges have to be overcome first. For example, the pedicles screws could not be placed strictly perpendicular due to anatomic limitations, resulting in distraction of the dorsal part and compression of the ventral part of the IVD. Also, a pedicle screw-rod fixation technique was used that was designed to fix a spinal motion segment permanently. A secondary invasive surgery to remove the pedicle screws and rods was needed. Also, an unquantified amount of distraction was applied during placement of the pedicle screw-rod fixation. An external device, consisting of pedicle screws placed under fluoroscopic guidance, combined with a calibrated spring to achieve a constant controllable distraction force could be established as an alternative technique, as these implants can be removed in a minimal invasive procedure. However, none of these devices customized to the canine spine are available yet. This pilot study is a starting point, but its clinical efficacy needs to be investigated in future studies with longer follow up times and more patients. Also, financial and ethical borders need to be crossed by dog owners which makes future studies quite a challenge.

Another therapeutic strategy to improve the outcome in patients with DDD focuses on restoration of spinopelvic parameters. Many spinopelvic parameters have been used to describe the sagittal alignment of the spine and new parameters are still added. However, there is still no consensus which parameter should be used due to lack of evidence. It also remains debatable, as changes in these parameters could also be part of the natural aging of the spine and thereby constitute for age-adjusted normative values. For example, strong correlation between increase of SVA and age ($r=0.46$, $p<0.001$) without increase of back pain and disability are described in the literature (48). In **Chapter 8**, a systematic review and meta-analysis of the literature was performed to analyze the correlations between spinopelvic parameters and clinical outcome. Unfortunately, all included studies were observational studies and in most of the studies the sagittal alignment was not actively and deliberately changed other than as a by-effect of the surgery. This means that the correlation could be confounded by other conditions that were treated such as painful spondylolisthesis. On the other hand, the results of the regression analysis indicated a correlation between improved surgical alignment and decreased disability and pain suggesting a

causal relationship. This meta-analysis therefore constitutes the current best evidence of a correlation between improved spinopelvic parameters after spinal fusion surgery. In evaluation of spinal sagittal alignment, acknowledgement of compensating mechanisms is crucial. The reciprocal association between pelvic parameters has a key role in the evaluation of these mechanisms. Because of the minimal motion that is possible in the sacro-iliac joint, PI, PT and SS can be mathematically linked, following a formula: PI=PT+SS (49). Although the PI slightly increases during growth, it stays relatively constant during adulthood (50). Pelvic retroversion (increase of PT and decrease of SS) is a compensatory mechanism that allows the patient to maintain a balanced standing posture with other radiological spinal parameters within normal range. Therefore the PT is more sensitive to malalignment. Indeed, in **Chapter 8**, the change in PT was found to be the most strongly correlated radiological parameter. Decrease of PT was significantly related to improvement in ODI and VAS. This key element is even clearer in patients that are not able to increase their PT due to hip osteo-arthritis and therefore have a significant greater risk of a disturbance in their sagittal spinal-pelvic alignment (51).

To improve the quality of research, standard clinical outcome parameters should be used in future studies so correlation analysis can be performed. For example, the RMDQ and ODI are two frequently reported PROMS. A previous systematic review compared the measurement properties of the RMDQ with the ODI and stated that there are no strong reasons to prefer the RMDQ or the ODI in patients with nonspecific low back pain (20). The focus in our analysis **(Chapter 9)** was not to assess whether one of the two instruments has better measurements properties, but to assess if they can be used exchangeable. Unfortunately, our results showed that the ODI and RMDQ are not exchangeable. Therefore, consensus on their use in clinical practice is essential to analyze treatment outcomes and provide sufficient patient counseling. The development of national registries with standard validated PROMs could help to gain sufficient data. For example, both the NASS and the Dutch Spine Society (DSS) have already incorporated the ODI into their registries. The international consortium for health outcome measurement (ICHOM) also recommends the ODI as the standard outcome measure for patients with low back pain. Therefore, in our opinion the ODI should be used in future clinical studies.

Conclusions

In this thesis, we tried to address several challenges in the treatment of patients with DDD. First of all, it was shown there is a challenge in achieving consensus within the spinal community in the Netherlands. Comparison between treatments is difficult due to a variety of clinical and radiographic outcome scores being used in daily practice, for which clear guidelines need to be constructed. We advise to use the ODI as standard clinical outcome parameter. Secondly, in search of alternative implant material to achieve solid fusion, it was found that the topographical surface features of abiotic materials may be at least as important as their surface chemistry. Future studies focusing on a combination of implant materials with a Young`s modulus that closely mimics the elastic modulus of bone, and that provides an optimal rough- and porous surface are needed. Thirdly, temporary distraction of a degenerated IVD might offer an alternative treatment option by preventing further degeneration of the involved disc and even affecting adjacent segment changes that may otherwise be triggered by a fused level. Lastly, decrease of PT was significantly related to improvement in ODI and VAS.

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11

SUMMARY IN DUTCH – NEDERLANDSE SAMENVATTING

Nederlandse samenvatting

84% van de bevolking krijgt gedurende zijn leven te maken met lage rugklachten, waarmee dit behoort tot een van de meest voorkómende gezondheidsproblemen ter wereld. Degeneratieve afwijkingen van de tussenwervelschijf kunnen hieraan ten grondslag liggen. Deze kunnen zorgen voor instabiliteit en daarmee pijn in de lage rug, en tot vernauwingen in de rug met zenuwbeklemmingen en uitstralende pijn in het been als gevolg. Een spondylodese is een veelgebruikte en succesvolle operatie indien conservatieve methodes falen. Hierbij wordt de degeneratieve tussenwervelschijf verwijderd en vervangen door een implantaat (cage), met als doel om de boven- en onderliggende wervels aan elkaar te laten vastgroeien (fusie) om zo de stabiliteit van het wervelsegment te herstellen. Om deze fusie te bevorderen worden verschillende typen cages en materialen gebruikt. Er zijn meerdere methodes in omloop die de klinische uitkomst en de mate van radiologische fusie bepalen na een spondylodese. Dit maakt het onderling vergelijken van de verschillende behandelopties en cages lastig. Er is echter geen breed gedragen overeenstemming (consensus) dat een radiologische fusie daadwerkelijk leidt tot betere klinische uitkomstmaten. Daarnaast zijn pseudoartrose (non-union) en slijtage van de omliggende wervelsegmenten (adjacent segment disease) belangrijke complicaties na een spondylodese. Het is dan ook van belang om meer kennis hierover te vergaren.

De studies gepresenteerd in dit proefschrift hebben als doel om de huidige behandelopties te evalueren en nieuwe strategieën in de behandeling van patiënten met symptomatische degeneratieve afwijkingen van de lage rug te analyseren. In **Hoofstuk 1** (Introduction) zijn hiervoor verschillende onderzoeksvragen geformuleerd, die onderverdeeld zijn in meerdere delen. In deel 1 evalueren we de huidige praktijk van de wervelkolomchirurgie in Nederland. In deel 2 wordt een nieuwe keramisch materiaal voor een cage (Silicon Nitride) onderzocht middels een dierstudie en een dubbel geblindeerd gerandomiseerde studie. In deel 3 focussen we op alternatieve behandelstrategieën, waaronder een tijdelijke distractie behandeling van de tussenwervelschijf en de rol van de sagittale balans op de functionele uitkomsten na een spondylodese. Tevens worden twee veel gebruikte patiënt gerapporteerde uitkomstmaten (PROMs) met elkaar vergeleken, om te analyseren of deze uitwisselbaar zijn en zo het vergelijken van uitkomsten van verschillende behandelstrategieën vereenvoudigen.

Deel I. Huidige praktijk

Er is momenteel veel variatie in Nederland binnen het gebied van operatietechnieken voor een spondylodese bij degeneratieve afwijkingen van de lumbale wervelkolom. Om de huidige praktijk omtrent indicatie, techniek, implantaten/gebruikte materialen en nabehandeling beter in beeld te krijgen, ontwikkelden wij een nationale enquête voor alle wervelkolomchirurgen in Nederland. De resultaten van deze enquête worden besproken in **Hoofdstuk 2**. Het meest gebruikte materiaal voor cages bij een spondylodese is polyetheretherketone (PEEK), gevolgd door titanium. Er is onderling geen consensus over de beste methode voor het bepalen van de mate van fusie. Daarnaast gebruikt slechts 62% van de respondenten standaard PROMs voor het meten van de klinische uitkomsten. De Visual Analoque Scale (VAS), Oswestry Disability Index (ODI) en Roland Morris Disability Questionairre (RMDQ) zijn de meest gebruikte PROMs.

Vervolgens is in **Hoofdstuk 3** met een systematisch literatuur onderzoek gekeken wat het bewijs is voor de huidige dominantie van de PEEK cage binnen de wervelkolomchirurgie. In totaal werden er 223 studies geïdentificeerd, waarvan slechts 10 studies konden worden geïncludeerd die voldeden aan de inclusie criteria (twee gerandomiseerde studies, 5 prospectieve en 3 retrospectieve studies). Er zijn geen verschillen gevonden tussen het gebruik van PEEK, titanium en andere type cages wat betreft klinische uitkomsten en mate van fusie. Aangezien er slechts een gelimiteerd aantal studies over de lumbale wervelkolom beschikbaar waren, met daarbij een grote variatie (in gebruikte techniek, type cage, radiologische metingen, PROMs en methodologie) zijn in dit systematisch literatuur onderzoek alleen studies over de cervicale wervelkolom meegenomen. Biomechanisch gezien is echter de verwachting dat verschillen in klinische uitkomsten en fusie percentages met name in de lumbale wervelkolom aan te tonen zullen zijn. Onderzoekers moeten daarom meer gestimuleerd worden om methodologisch goed onderbouwde lumbale studies te publiceren, waarbij wordt geadviseerd om standaard PROMs en radiologische uitkomstmaten te gebruiken om zo de kwaliteit van de studies te verbeteren en de resultaten van deze studies onderling te kunnen vergelijken.

Deel II. Uitdagingen in fusie technieken: de SNAP trial

Ondanks dat de PEEK cage het meest gebruikte materiaal in Nederland is voor een spondylodese ("gouden standaard"), worden complicaties zoals non-union, migratie en verzakking van de PEEK cage in de omliggende wervel (subsidence) gezien. Een adequate osteointegratie (het direct ingroeien van bot op het oppervlak van de cage) kan hierbij van belang zijn, om zo een solide fusie te bewerkstelligen. Doordat PEEK een hydrofoob (waterafstotend) oppervlak heeft vormt er zich eerst een fibreuze weefsel laag op het oppervlak van de cage, waardoor directe botingroei niet mogelijk is en de osteointegratie verstoord wordt. Daarnaast is PEEK niet goed zichtbaar op röntgen en CT beelden, waardoor de mate van botingroei op het oppervlak van de cage moeilijk te bepalen is. Een alternatief is Silicon Nitride (Si_3N_4), een keramisch materiaal met goede osteointegratieve en mechanische eigenschappen, zoals aangetoond in meerdere *in vitro* en *in vivo* studies. Daarnaast is Si_3N_4 goed zichtbaar op röntgen, CT en MRI beelden. De verwachting is dan ook dat de Si_3N_4 cage minder complicaties en betere klinische en radiologische uitkomsten genereert. Er zijn nog geen studies bekend waarin de ``gouden standaard`` PEEK cage met de nieuwe Si_3N_4 cage wordt vergeleken.

In **Hoofdstuk 4** zijn daarom in een dierenstudie de resultaten vergeleken tussen deze twee implantaten. Hiervoor is een geitenmodel gebruikt. Zes maanden na een lumbale spondylodese werd in 87.5% bij zowel de PEEK als de Si_3N_4 cage een volledige fusie tussen de wervels gezien. Wel was er significant meer botvolume rondom de Si_3N_4 cage dan bij de PEEK cage (52.6% vs 27.9%). Histologische analyses laten zien dat op het oppervlak van zowel PEEK als Si_3N_4 fibreus weefsel overheerst boven botweefsel. Biomechanische analyses tonen verder geen verschil in beweging (flexie/extensie, lateroflexie en rotatie) tussen de gefuseerde niveaus van PEEK en Si_3N_4. De resultaten van deze geitenstudie laten de potentiele meerwaarde van Si_3N_4 zien.

Om de verschillen in de klinische setting bij patiënten tussen beide materialen verder te onderzoeken, is de SNAP studie (Silicon Nitride And PEEK) ontworpen, waarvan in **Hoofdstuk 5** het studie protocol is gepresenteerd. De studie is ontworpen als een dubbelblind (patiënt en onderzoeker) multicenter gerandomiseerd onderzoek, waarin 100 patiënten met chronische lage rugklachten op basis van degeneratieve afwijkingen een lumbale spondylodese met een PEEK of een Si_3N_4 cage ondergaan.

De data in **Hoofdstuk 6** beschrijven de lange termijn resultaten van de SNAP studie. Gedurende de 2 jaar follow-up laten beide patiëntengroepen (PEEK en Si_3N_4) goede en vergelijkbare klinische verbetering zien in PROMs (RMDQ, SF36, ODI en VAS scores). Er zijn geen significante verschillen gemeten in de mate van radiologische fusie (middels röntgen, CT en flexie/extensie opnames) en klinische uitkomstmaten tussen de twee verschillende type cages. Er waren echter meer peri-operatieve complicaties en revisies binnen de Si_3N_4 groep. Concluderend, hoewel theoretisch de verwachting was dat de Si_3N_4 cage significant betere uitkomstmaten zou genereren, zijn de resultaten van de Si_3N_4 cage in de klinische setting vergelijkbaar met de PEEK cage. Meerdere factoren zijn hierbij van invloed. Naast de chemische samenstelling spelen de topografische kenmerken van het oppervlak van de cage een belangrijk rol. Toekomstige studies zijn nodig waarin een combinatie van de juiste elasticiteit (zo dicht mogelijk bij die van bot) en adequate topografische kenmerken van het materiaal (ruw en poreus) wordt onderzocht. 3D geprinte cages bieden op deze vlakken veel potentie.

Deel III: Uitdagingen in andere therapeutische strategieën

Naast de zoektocht naar alternatieve materialen om de osteointegratie te bevorderen, worden er ook andere strategieën onderzocht om de uitkomst van behandeling van patiënten met lage rugpijn en degeneratieve afwijkingen te verbeteren. In patiënten met degeneratieve knieën en enkels laat tijdelijke distractie (het uiteen trekken van het gewricht) goede resultaten zien, waarbij verdere kraakbeenschade tijdelijk kan worden voorkomen. Aangezien er overeenkomsten zijn tussen gewrichtskraakbeen en de tussenwervelschijf in de rug, zou tijdelijke distractie van een versleten wervelsegment mogelijk verdere degeneratie van de tussenwervelschijf en slijtage van de omliggende wervelsegmenten kunnen verminderen. Om de veiligheid en effectiviteit van tijdelijke distractie van de tussenwervelschijf verder te onderzoeken, wordt in **Hoofdstuk 7** een onderzoek beschreven bij een hond met klinische en radiologische degeneratieve afwijkingen van de tussenwervelschijf. Met een pedikelschroef systeem is gedurende 3 maanden een distractie verricht van de tussenwervelschijf op niveau L7-S1, waarna de schroeven met een tweede operatie zijn verwijderd. De functionele status van de hond is gemeten door middel van force-plate analyse. De hoogte en oppervlakte van de tussenwervelschijf zijn met MRI (T2) en standaard röntgen opnames gemeten als maat voor degeneratie. Deze studie heeft aangetoond dat een tijdelijke distractie

van de tussenwervelschijf veilig is en klinische verbetering geeft (4% ten opzichte van pre-distractie). Daarnaast verslechterd de radiologische mate van degeneratie niet tot 6 maanden na distractie. Het biedt een nieuw inzicht in de behandeling van patiënten met symptomatische degeneratieve afwijkingen van de lage rug. Echter, om te bepalen of deze behandeling effectief is zullen langere termijn resultaten verder uitgezocht moeten worden in grotere groepen patiënten, alvorens dit in de praktijk te kunnen brengen.

Binnen de wervelkolomchirurgie is er steeds meer aandacht voor het herstel van de sagittale balans van rug en bekken, om zo betere klinische uitkomsten te genereren na operatie. In **Hoofdstuk 8** is deze theorie verder uitgezocht middels een uitgebreid systematisch literatuur onderzoek. Er werden 2024 artikelen gevonden, waarvan er op basis van de inclusiecriteria er uiteindelijk 34 konden worden geïncludeerd. Om de sagittale balans en de impact op de klinische uitkomst te analyseren zijn in deze geïncludeerde studies negen verschillende PROMs en tien verschillende radiologische uitkomstmaten beschreven. Door middel van een meta-analyse van de data zijn uiteindelijk twee significante correlaties gevonden tussen radiologische metingen en PROMs: een lagere postoperatieve kanteling van het bekken (pelvic tilt) is gecorreleerd met minder pijn, en een lagere postoperatieve kanteling van het bekken (pelvic tilt) is gecorreleerd met een betere ODI score. Deze studie toont, naast de rol van de sagittale balans, ook het belang aan om standaard klinische en radiologische uitkomstmaten te gebruiken in toekomstige onderzoeken, om zo de willekeur aan uitkomstmaten in te perken en de kwaliteit van de studies te verbeteren.

Hierop voortbordurend, zoals eerder beschreven in Hoofdstuk 2 zijn de twee meest gebruikte PROMs voor patiënten met lage rugklachten de ODI en de RMDQ. Beide worden door elkaar gebruikt naar gelang de voorkeur van de operateur en onderzoeker. Dit maakt het vergelijken van uitkomsten van verschillende behandelstrategieën moeizaam. In **Hoofdstuk 9** is daarom onderzocht of de ODI en RMDQ uitwisselbaar zijn. Hiervoor zijn de klinische data van patiënten uit de SNAP studie gebruikt, met in totaal 376 vragenlijsten (ODI en RMDQ) . Na een uitgebreide statistische analyse (oa Spearmann correlaties en Bland Altman plot) blijkt er, ondanks een zeer sterke correlatie ($r=0.87$, $p=0.001$) onvoldoende overeenkomst tussen beide PROMs, waarmee geconcludeerd wordt dat deze PROMs niet uitwisselbaar zijn. Deze

studie onderstreept het belang van duidelijke richtlijnen voor het gebruik van PROMs. Nationale registers met standaard gevalideerde PROMs kunnen hierbij behulpzaam zijn. De Dutch Spine Society (DSS) en de North American Spine Society (NASS) hebben hier reeds goede stappen in gemaakt, en adviseren om de ODI te gebruiken als standaard PROMs.

APPENDICES

LETTER TO THE EDITOR

ACKNOWLEDGEMENTS/
DANKWOORD

CURRICULUM VITAE

TO THE EDITOR: TWO-YEAR RESULTS OF A DOUBLE-BLIND MULTICENTER RANDOMIZED CONTROLLED NON-INFERIORITY TRIAL OF POLYETHERETHERKETONE (PEEK) VERSUS SILICON NITRIDE SPINAL FUSION CAGES IN PATIENTS WITH SYMPTOMATIC DEGENERATIVE LUMBAR DISC DISORDERS

Kersten RFMR, Öner FC, Arts MP, Mitroiu M, Roes KCB, de Gast A, van Gaalen SM
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Unpleasantly surprised we read the study by McEntire, Maslin and Bal (1). As the principal investigators of this study, comprising of the surgeons and staffs of the participating hospitals, we did not authorize the authors to publish these results. We strongly disagree with the post-hoc analysis performed by the authors, and therefore terminated our prior collaboration with McEntire *et al* during the review process of this study. The correct version of the manuscript, discussing the authentic one and two-year results of our RCT, has recently been published in The Global Spine Journal (2). The original protocol criteria were used to analyze these results, published in 2014 (3).

McEntire and Bal are involved in SINXT Technologies (formerly known as Amedica), the manufacturer of the silicon nitride interbody cage. Our collaboration with Amedica started in 2011 with the design of the Silicon Nitride versus Peek (SNAP) trial, resulting in a joint publication of the SNAP research protocol (3). Furthermore an *in vivo* caprine study of silicon nitride versus PEEK cages was published with mutual consent (4). Amedica acted as the sponsor of these studies. An independent clinical research organization (CRO) managed the clinical trial together with the principal investigator's institutions. After analyzing the one and two-year results of our clinical RCT, we concluded there is insufficient evidence that the silicon nitride cage is non-inferior to the PEEK cage, using the original protocol criteria. Amedica (now called SINXT Technologies) disagreed, and presented a biased post-hoc analysis confirming the non-inferiority of silicon nitride compared to PEEK. Also, they excluded the principal investigators to publish their view of the results of the RCT by claiming

exclusive rights for the study data. With this act, the authors did not adhere to the ethical and moral standards of Evidence Based Medicine (EBM). Firstly, they acted contrary to article 36 of the Declaration of Helsinki, stating "Negative and inconclusive as well as positive results must be published or otherwise made publicly available". Also, restricting the principal investigators to publish the authentic results is deemed to be unreasonable according to the involved Medical Ethics Committee (METC) Directive on the Assessment of Clinical Trial Agreements. Moreover, the authors did not adhere to the revised International Committee of Medical Journal Editors (ICMJE) criteria. Lastly, it discloses a case of plagiarism by copying large parts of the Introduction, Methods, Results and Discussion sections combined with the figures and tables of the principal investigators (2).

Methodologically, their post-hoc analysis approach is a clear case of incorrect scientific practice. The design of the study (3), including the non-inferiority margin and assumptions, provided ample opportunity to challenge the margin and assumptions prior to having access to unblinded data and results. This did not happen, it only occurred at the moment the authors were fully aware of complete results. Their reasoning on what constitutes a non-inferiority margin is flawed: this margin is not the minimal clinically important difference (MCID) at individual patient level, but a margin that ensures non-inferiority at population level, as well as that it is sufficiently small to be robust against constancy of effects over time (5,6). Likewise, statistical power assessments at the design stage include that the standard deviation is not fixed but is estimated from the data. Post-hoc "power" calculations based on the observed standard deviation can be done, but they do not constitute an assessment of power of the study (7,8). The post-hoc analysis is fully data driven, therefore actual type 1 error (significance level) cannot be assessed and is likely inflated. The possibility to evaluate the primary results against any other non-inferiority margin than pre-defined is already perfectly possible based on our published paper (2) and does not justify an independent paper.

The EBM primary goal is to increase our scientific knowledge in order to improve public health and patient's care. However, SINXT Technologies did not act in the patients' best interest. In our opinion they have shown to be an unreliable partner and potentially damaged the public debate about interactions between commercial

entities and research institutions. We strongly urge the editor to remove the publication of McEntire *et al* from the Journal of Spine Surgery and all publicly available platforms and when deemed necessary take any further legal steps.

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Curriculum Vitae

Roel Kersten (January 1985, Teteringen) grew up in Breda with two older sisters and attended highschool at the Stedelijk Gymnasium Breda. After graduating in 2003, he started medical school at the Rijksuniversiteit Groningen (RUG). During this time he developed an interest in orthopedics, which led him to the orthopedic surgery department of the University Medical Center Groningen as a student researcher (supervisor: dr. I. van den Akker-Scheek). In his final year in medical school he moved to Amsterdam with Sophie, the love of his life, who he met in Groningen. After completing his senior internship at the department of orthopedic surgery at the OLVG in 2011, he started as a non-training resident/researcher at the department of orthopedic surgery at the Diakonessenhuis (supervisor: dr S.M. van Gaalen). Here he laid the foundation of this thesis, which resulted in a PhD trajectory in 2013 under supervision of prof. dr. F.C. Öner, dr S.M. van Gaalen and dr. M.P Arts.

In 2014 he started with his residency in orthopedic surgery, during which he continued his research for this thesis. He completed the first part of his training at the general surgery department of the St. Antonius Hospital (supervisor: dr. P.M.N.Y.H. Go). He continued his orthopedic surgery training at the University Medical Center Utrecht (supervisor then: prof. dr. D.B.F. Saris), the St. Antonius Hospital (supervisor: dr. M.R. Veen), returned to the Diakonessenhuis (supervisors: dr. A. de Gast and dr. A.W. Zürcher), and completed his residency at the University Medical Center Utrecht in 2020 (supervisor: prof. dr. J.J. Verlaan).

During his residency, he developed a special interest in arthroplasty and sports trauma of the lower extremity. Therefore, after registering as an orthopedic surgeon, he returned up north and commenced a fellowship knee surgery at the Martini Hospital Groningen (supervisor: dr. R.W. Brouwer), where he still currently works. He keeps enjoying the good life in Amsterdam, where he lives together with his wife Sophie and their children Evie (2015) and Boris (2018).