Long-term follow-up of total lumbar disc replacement

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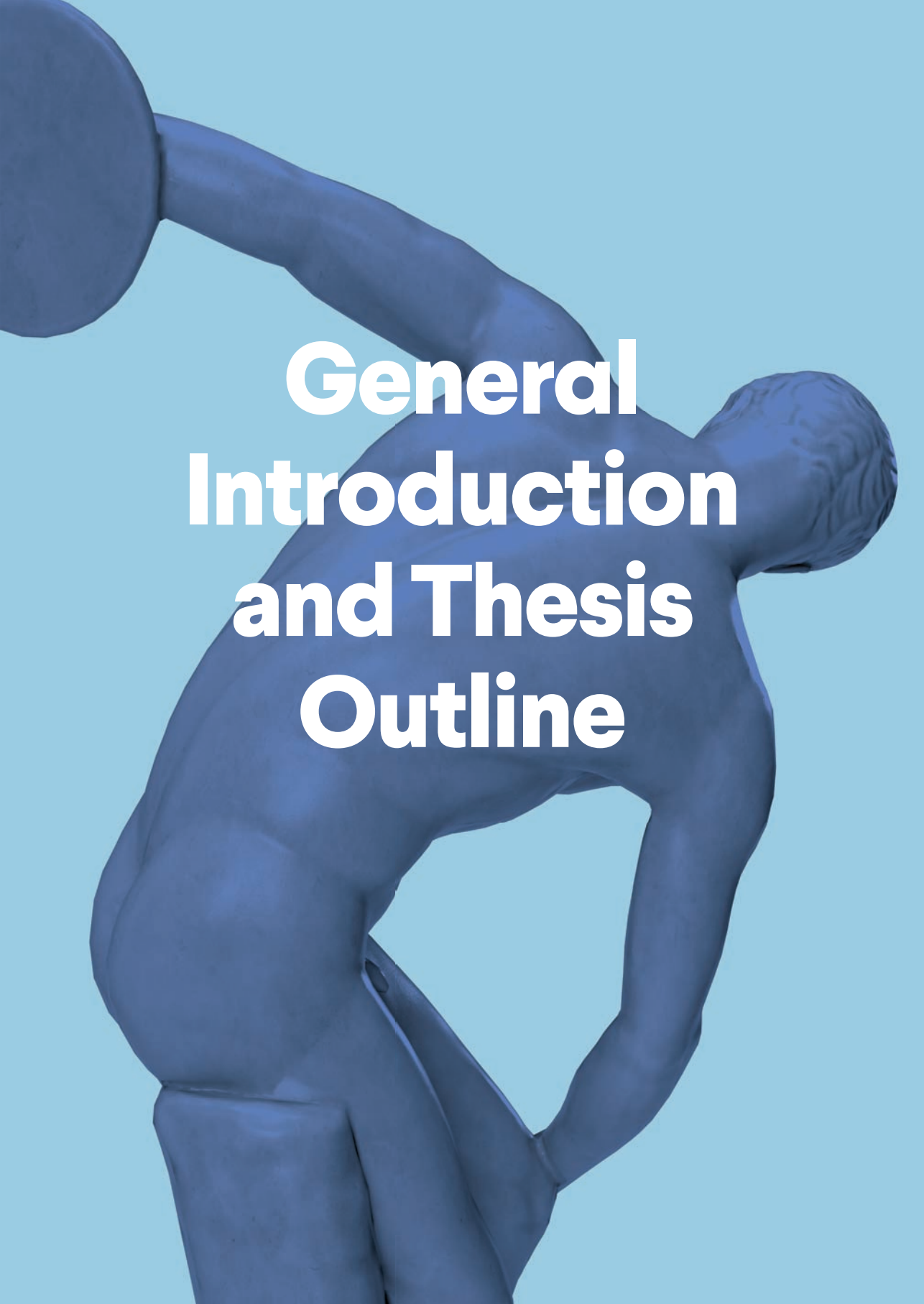

General Introduction and Thesis Outline

Introduction

Epidemiology of low back pain

Chronic low back pain (LBP) is one of the most common disabling conditions in the Western society, resulting in substantial economic costs related to the utilization of healthcare resources and immense indirect costs by disability and productivity losses.[1,2] In the Netherlands, it is estimated that the direct health care costs related to back pain exceed 1.3 billion euros.[3] Moreover, the indirect cost of lost productivity due to work absenteeism and early retirement were estimated to be up to ten times higher than the direct costs.[4,5] Globally, chronic LBP was responsible for 60.1 million disability-adjusted life-years in 2015, an increase of 54% since 1990 with the biggest increase seen in low- and middle-income countries.[6] The Global Burden of Disease Program was initiated to investigate the worldwide impact of different diseases on health status and disability.[7] For all diseases studied, the highest degree of disability, as measured by patient health status preferences, was found for (chronic) LBP.[8] Moreover, the global burden of chronic LBP is projected to increase even further in coming decades.[6]

Spinal anatomy in relation to the intervertebral discs

The human body relies on the spinal column for the main musculoskeletal axis of support, for mobility at the segmental level, and to protect the spinal cord from injury. Adjacent vertebrae articulate through the superior and inferior facets of the vertebral articular processes, as well as through fibrocartilaginous intervertebral disc joints between the vertebral bodies. Two adjacent vertebrae with the intervertebral disc, facet joints, and adjoining ligaments form a functional spine unit.[9,10] (Figure 1.1)

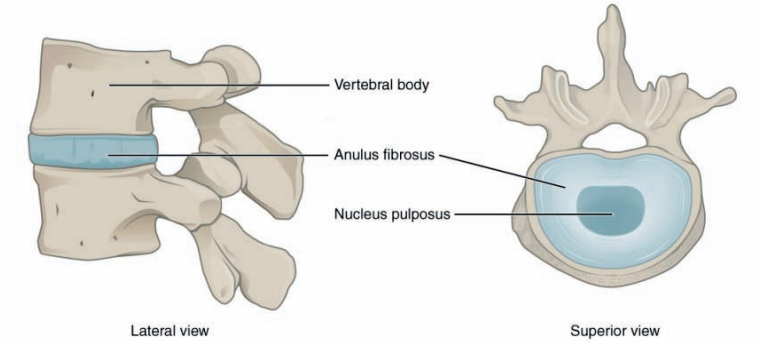

Figure 1.1 Spinal anatomy in relation to the intervertebral disc on lateral and superior view.

The intervertebral disc consists of an inner core, the nucleus pulposus, surrounded by an outer ring, the annulus fibrosus. The nucleus pulposus is a gel-like structure in the center of the intervertebral disc and is capable of resisting high loads while maintaining

flexibility of the spine. It is made of 66% to 86% of water with the remainder consisting of primarily type II collagen and proteoglycans. The annulus is a ring-shaped disc of fibrous connective tissue that surrounds the nucleus pulposus. The annulus contains an inner and an outer portion. They differ primarily in their collagen composition. While both are primarily collagen, the outer annulus contains mostly type I collagen, while the inner has predominantly type II.[10,11]

The nucleus pulposus serves to distribute hydraulic pressure throughout the intervertebral disc. By virtue of its high-water content, the nucleus pulposus can disperse the forces placed on one aspect of a vertebral body to the entire structure, thus decreasing the risk of trauma of the vertebral body. The annulus encircles the nucleus pulposus to provide structure to the gelatinous form. Consequently, the intervertebral discs allow for the spine to be a supportive, yet flexible structure.[10,11]

Degeneration of the spine is thought to initiate with biochemical changes in the intervertebral disc followed by macroscopic alterations such as tears and fissures. These changes may ultimately lead to disc herniation and disc degeneration.[9,12] Subsequent degeneration occurs in the facet joints with cartilage alteration, osteophytosis, and subluxation.[9,12] Degenerative Disc Disease (DDD) is an inevitable process of aging, but it seems that genetic predisposition plays an important role.[13,14] DDD occurs at variable rates and to variable degrees in different individuals and may be asymptomatic.[9,12] However, it is postulated that DDD can be a source of chronic LBP.[5,15-17]

Histological studies have revealed abnormal ingrowth of sensory nerve endings in the nucleus pulposus and bony endplates in patients with a degenerative lumbar disc.[18] In addition, an ingrowth of free nerve endings (nociceptors) and blood vessels with a granulation zone releasing pro-inflammatory mediators and cytokines, is linked to radial fissures in the annulus fibrosis.[19-21] These findings suggest that DDD could contribute to chronic LBP, with or without secondary facet joint changes. Therefore, it is postulated that this “discogenic pain” is exacerbated by continued motion at the affected level and operative treatment might be beneficial in patients with lumbar DDD not responding to conservative care.

Controversy regarding Degenerative Disc Degeneration

Fusion of a symptomatic lumbar spinal motion segment is the most commonly used operative treatment for patients with DDD not responding to conservative care.[22-24] However, the efficacy of surgery over nonoperative treatment for patient suffering from severe chronic LBP assumed to be caused by DDD at the lower lumbar levels is still very much under debate.[16,17] Conservative treatment may consist of physiotherapy or - in case of psychosocial problems - of multidisciplinary cognitive-behavioral and exercise rehabilitation to improve functional disability.[16,17]

A systematic review by Philips et al.[17] concluded that fusion surgery is a viable treatment option for reducing pain and improving function in patients with chronic LBP refractory to nonsurgical care when a diagnosis of DDD can be made. On the other hand, a systematic review by Mannion et al.[16], concluded that there was no difference in patient self-rated outcomes between fusion and multidisciplinary rehabilitation for patients suffering from chronic LBP assumed to be caused by DDD. To their opinion, given the increased risks of surgery and the lack of deterioration in nonoperative outcomes over time, the use of lumbar fusion for patients with chronic LBP by DDD should not be favored.

Lumbar Total Disc Replacement (TDR) has gained popularity since the early 1990s as an alternative for fusion in patients with chronic LBP assumed to originate from DDD. A randomized controlled multicenter trial by Furunes et al.[25], assigned 173 patients with chronic LBP and DDD to either TDR or multidisciplinary rehabilitation. At 8-years follow-up, a statistically significant difference of the Oswestry Disability Index score (ODI) was found in favor of surgery, but smaller than the prespecified clinically important difference of 10 ODI points that the study was designed to detect.[25]

History and design of the SB Charité III TDR

The SB Charité III TDR (Waldemar Link, Germany; DePuy Spine, Raynham, MA) was designed with the aim to mimic the kinematics of the native vertebral disc.[26,27] The SB Charité TDR has a bi-convex sliding mobile ultra-high molecular weight polyethylene (UHMWPE)-core, which articulates against two concave cobalt-chrome-molybdenum endplates. This unconstrained design essentially relies on the same principles as many total hip replacements, namely polyethylene-on-metal articulation.[26,27] (Figure 1.2)

Figure 1.2 Example of SB Charité III TDR.

The two main design concepts for TDR include semi-constrained and unconstrained implants. The unconstrained implants allow translation of the mobile core and reduce stress concentration at specific points on the bearing surfaces.[28-30] These implants rely on surrounding structures to provide restraint to more extremes in the range of motion (ROM). This may lead to greater stress to the facet joints compared to the semi-constrained implants, since these devices have a fixed axis, possibly reducing the load on the facet joints.[28-30] However, biomechanical studies have demonstrated for both designs an increased facet joint pressure and altered loading patterns after TDR.[31-34]

The SB Charité III was the first TDR that was implanted on a large scale.[27,35] It was launched internationally in 1989. In 2004 the SB Charité III TDR was approved for clinical practice by the Food and Drug Administration (FDA) in the USA.[35] Between its release and the approval by the FDA, a number of changes have been made to the sterilization and packaging process of the UHMWPE. In addition, in 1998 a bioactive hydroxyapatite coating of the prosthetic endplates was introduced. The aim was to stimulate bony ingrowth and consequently reducing migration or subsidence of the TDR. Although the Charité TDR is since 2012 no longer being implanted due to decreasing sales and the acquisition of the company Synthes (manufacturer of the Pro-Disc TDR) by DePuy, the basic design features of the TDRs used today in clinical practice, are still very much comparable.

Survival of the TDR

Spinal fusion is associated with negative side effects such as cranial facet-joint violation, pseudarthrosis, and symptomatic adjacent segment disease (ASD).[36-39] TDR has been introduced to avoid these fusion-related side-effects based on the hypothesis that chronic low LBP originates from DDD. However, TDR has also been associated with drawbacks, such as subsidence, dislocation or malposition of the implant, decreased axial rotational stability, and excessive loads to the facet joints leading to facet joint arthritis.[40-42]

Data from randomized controlled trials with a follow-up of five years, indicate that TDR at mid-term follow-up is not inferior to spinal fusion with reoperation rates of 7.7-16.2% for TDR and 8.3-16.3% for spinal fusion.[22-24] A systematic review of overlapping meta-analyses on TDR versus fusion for lumbar DDD from Ding et al.[43] reported that the current best available evidence suggests that TDR may be an effective technique for the treatment of a select group of patients with lumbar DDD, and is at least equal to lumbar fusion in the short term. However, considering that disadvantages may appear after years, spine surgeons should be cautious about performing TDR on a large scale.[43]

In a Cochrane meta-analysis by Jacobs et al.[41] an average reoperation rate of 7.8% at 2 to 5-years follow-up was found for patients with a TDR. However, to assess the concerns

on the survival of the TDR, the accumulation and analysis of long-term data are paramount. As yet, there are few studies with a minimal follow-up of at least 10-years reporting on these issues.[44-49] A lack of a control group (either nonoperative or index spinal fusion) can be attributed to all these studies. They describe a reoperation rate between 6-33% after an average of 11-years follow-up. Approximately 5-14% of the patients had revision fusion surgery, with or without removal of the TDR.[44-49]

A study by Punt et al.[50] compared periprosthetic tissue reactions observed after TDR and total hip replacement (THR). They reported that despite the differences in loading and kinematics between the lumbar spine and the hip joint, the mean wear particle size and shape were comparable between TDR and THR. Although the tissue concentrations of wear particles after TDR revision were lower compared to those after THR, it might initiate the same inflammatory response leading to osteolysis as seen in THR after longer follow-up.

In a study in the Lancet published in 2019 by Evans et al.[51], which consists of a systematic review and meta-analysis of case series, as well as national registry reports with more than 15-years of follow-up, it was investigated how long a THR would last. From this study we learned that to truly asses the number of late revisions of an implant, at least 15-years of follow-up is warranted, ideally even 20-years or more. They reported a pooled analysis of all-cause survivorship of the THR of 85.7% at 15-years, with a drop to 78.8% at 20-years, reaching a plateau at 25-years with 77.6%. Therefore, much debate remains on the use and effectiveness of TDR, in particular concerning fear of high rates of late loosening and revisions as seen after THR.[43]

Residual-mobility and the occurrence of ASD

TDR has been introduced in order to preserve motion at the affected level and mimic the morphology of the intervertebral disc,[27,52] with the overall aim to prevent the occurrence ASD as seen after lumbar fusion, and thus a presumably better long-term outcome.[53-56] A systematic review by Wang et al.[57] showed a pooled risk of clinical ASD that needed revision surgery of 1.2% and 7.0% in the TDR and fusion groups, respectively, after a maximum of 5-years follow-up. A RCT by Zigler et al.[58] reported significantly less intervertebral disc degeneration in the adjacent levels after TDR at five years follow-up. It is interesting to assess whether this protective effect against ASD, that TDR seems to have five years after the index surgery, will remain with longer follow-up. However, studies on this subject with a minimal follow-up of at least 10 years are scarce and report a reoperation rate for ASD ranging between 2% and 17%.[44,46,47] The predicted reoperation rate of ASD after spinal fusion ranges between 9.9% and 22.2% at 10 year follow-up.[55,59,60]

Presumably, the preservation of motion in the affected segment (residual-mobility), plays an important role in lowering the occurrence of ASD after TDR. Multiple studies with a follow-up ranging from 2 to 11 years, have shown that range of motion (ROM) was preserved[44,49,61-67] or even increased [46,61,68-80] after TDR. However, none of these studies evaluated residual-mobility in relation to the occurrence of ASD and clinical outcomes. An import point to consider is not only if there is motion, but rather whether it mimics physiological motion in the affected lumbar segment.

Biomechanical studies have shown that motion of a TDR differs from that of a normal disc in an intact spine.[81-83] These studies described an increase in rotational instability at the index TDR level. Other biomechanical studies have demonstrated an increased facet joint pressure and altered loading patterns after TDR.[31-34] The highest stress impact on the facet joints is seen with axial rotation, when compared with side bending and flexion/extension.[32] This confirms the important role of facet joints in limiting axial rotation and, considering the increased rotational instability, facet joint degeneration (FJD) might be accelerated after TDR.

In a study of Nunley et al.[84] pressure effects on adjacent level discs after 2-level constructs, i.e., fusion, hybrid, and TDR were compared. No significant differences were found between the different procedures. So presumably not so much the extent of motion (in degrees), but the quality of motion could be the main factor in the occurrence of ASD. Siepe et al.[42] reported a significant increase of facet joint degeneration (FJD) at the index level after TDR and a significant decrease in ROM at the same level. The occurrence of FJD was associated with significantly higher VAS- and ODI-scores. In this light, it is interesting to see if residual-mobility is still present after a longer follow-up, if this residual-mobility is protective against the occurrence of ASD, and if this is associated with clinical outcome

TDR and the occurrence of subsidence

Subsidence of TDR, defined as the penetration of the prosthetic endplate into the vertebral endplate, is a frequently occurring complication.[40,41,85-87] Subsidence occurs presumably due to non-central implantation,[75,88] implant undersizing,[89,90] or reduced bone quality.[91] Different methods have previously been described to quantify radiographic subsidence.[87,90] (Figure 1.3)
Subsidence may ultimately lead to spontaneous fusion of the vertebral segment or to failure of the TDR.[86] Consequently, patients with symptoms and radiographic subsidence, even without clear signs of wear or displacement, may undergo revision surgery. However, there are no studies describing a clear relation between the occurrence of radiographic subsidence and signs or symptoms of the patient. In addition, it is important to investigate if the occurrence of subsidence can be reduced by adapting the position and relative size of the TDR.

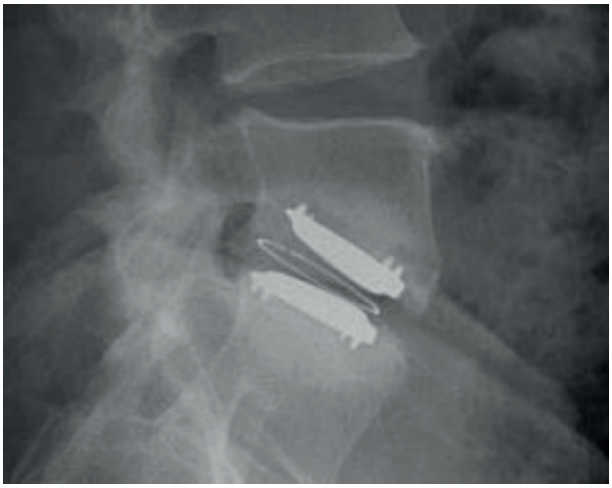

Figure 1.3 Example of SB Charité III TDR on level L4-L5.

Revision strategies

There is an ongoing discussion whether revision surgery for failed TDR is beneficial, and if so, what the optimal revision strategy should be.[92-95] More specific should a failed TDR be removed?

Research questions and thesis outline

1. What is the long-term survival of TDR using the Charité III prosthesis for patients with chronic LBB assumed to be caused by degenerative disc disease?

Controversy on the use and long-term effectiveness of the TDR for surgical treatment of lumbar DDD exists, especially concerning fear of high late revision rates. Therefore, the long-term clinical outcome in terms of patient satisfaction, complications and revision rates after TDR was examined in **Chapter 2.** Additionally, an assessment was made to identify patient- or surgery-related risk factors for revision or worse clinical or functional outcome.

2. What is the long-term incidence of ASD and residual mobility after TDR and are they related to clinical outcome?

TDR has been introduced in order to preserve segmental motion and thus reduce ASD as seen after lumbar spinal fusion. However, it is uncertain whether these presumed beneficial effects of TDR remain at long-term follow-up. In **Chapter 3** the long-term occurrence of ASD and residual-mobility after TDR was evaluated. Additionally, an assessment was made whether ASD and residual-mobility were related to clinical outcome.

3. Is subsidence of a TDR related to clinical outcome and can it be predicted by the position or relative size of the implant?

Patients with symptoms and subsidence, even without clear signs of wear or displacement, may undergo revision surgery. However, there are no studies describing a clear relation between the occurrence of radiographic subsidence and signs or symptoms of the patient. In Chapter 4 it was investigated to what extent subsidence over time is related to clinical outcome. A secondary goal was to investigate if subsidence could be predicted by the position and relative size of the TDR on the direct postoperative radiographs.

4. What are the long-term clinical results and complications of the different revision strategies for failed TDR?

There is an ongoing discussion whether revision surgery for failed TDR is beneficial, and if so, what the optimal revision strategy should be.[92-95] The purpose of **Chapter 5** is to compare the long-term clinical results (minimal follow-up of 5 years) and complications of posterolateral instrumented fusion combined with TDR removal versus stand-alone fusion.

Finally, **Chapter 6** comprises a discussion of the main findings of the previous chapters, addresses the current literature, provides final conclusions and recommendations.

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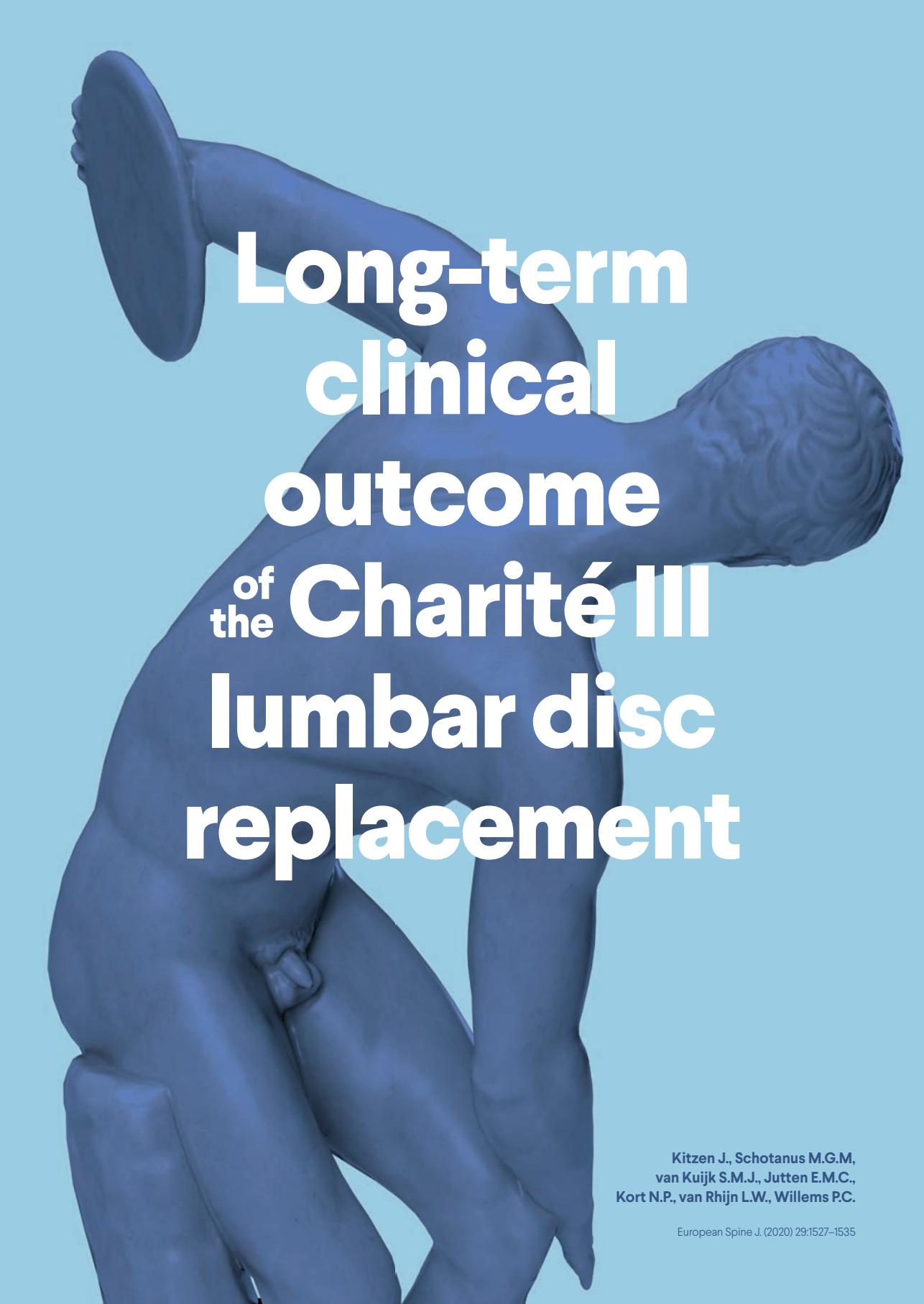

Long-term clinical outcome of the Charité III lumbar disc replacement

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Abstract

Purpose

Controversy on the use and long-term effectiveness of the TDR for surgical treatment of lumbar degenerative disc disease exists, especially concerning fear of high revision rates. The aim of this study was to evaluate the long-term clinical outcome and revision rates after total lumbar disc replacement (TDR).

Methods

405 consecutive patients treated with TDR from 1989 to 2000 were invited for evaluation. Data on reoperations were collected from the medical records. All patients who had undergone revision fusion surgery were scored as failures and from all those who had not been revised, Patient Reported Outcome Measures were obtained at latest follow-up.

Results

A total of 296 patients (73.1%) were available for evaluation. The mean follow-up after the index TDR was 19.4 years. The overall reoperation rate was 31.1% (n=92). In 59 of these patients (19.9%) spinal fusion at the index level was performed. Most of the fusion procedures (n=48, 81.4%) had occurred in the first 10-years after the TDR. Rheumatoid arthritis (p=0.004), osteoporosis (p=0.048), age at the time of surgery <45 years (p=0.031), BMI>30 (p=0.029), and previous spinal surgery (p=0.048) were all associated with worse clinical outcomes in terms of a Visual Analog Scale score for pain ≥5.0 or/and an Oswestry Disability Index score ≥40.

Conclusion

Fear of excessive late revision procedures following TDR could not be substantiated after a mean follow-up of 19.4 years. Proper patient selection considering the identified risk factors for worse outcome may help to improve the clinical and functional outcome in these patients.

Introduction

Fusion of a symptomatic lumbar spinal motion segment is still considered the gold standard for operative treatment of patients with degenerative disc disease (DDD) not responding to conservative care.[1-3] However, spinal fusion is associated with side effects such as cranial facet-joint violations, decrease in sagittal motion, pseudarthrosis, and symptomatic adjacent level disease.[4-7]

Total lumbar disc replacement (TDR) has been introduced to avoid those fusion-related side-effects based on the hypothesis that chronic low back pain (LBP) originates from DDD. However, TDR has also been associated with drawbacks, such as subsidence, luxation or malposition of the implant, increasing axial rotational instability and excessive loads to the facet joints.[8-10] In a meta-analysis an average reoperation rate of 7.8% at two to 5-years follow-up was found.[9] Several studies with mid- to long-term results reported that 6-14% of the patients had revision fusion surgery after TDR.[11-17]

Data from randomized controlled trials with a follow-up of five years have shown that TDR is not inferior to spinal fusion.[1-3] Nonetheless, much debate remains on the use and effectiveness of TDR, in particular concerning high rates of late loosening and revisions.[18] Mid- to long-term studies on this subject are scarce.[2,3,11-17,19] Only six studies have a mean follow up of 10-years or more.[11-14,16,17]

The purpose of this study was to evaluate the long-term clinical and functional outcome in terms of patient satisfaction, and complication and revision rate after TDR. Additionally, an assessment was made to identify patient- or surgery-related risk factors for revision or worse clinical outcome.

Materials and methods

Patient selection

The current study was approved by the Medical Ethics Committee METC Z (16-N-22) and registered at the Dutch Trial Registry (NTR5710). The medical records of all patients who had undergone a TDR by a single surgeon using a SB Charité III between 1989 and 2000 at the Zuyderland Medical Centre, Sittard-Geleen, the Netherlands, were reviewed. Altogether, 405 consecutive patients were identified.

TDR had been performed as treatment for patients with predominantly axial low back pain with failure of appropriate conservative measures and the presence of lumbar DDD as determined by plain radiographs and/or MRI. Preoperatively, all patients had

undergone fluoroscopically guided provocation discography to rule out non-discogenic pain sources. No facet joint injections were performed. Radiculopathy, spondylolisthesis, or spondylolysis were considered a contraindication for TDR. Patients with a previous discectomy or small decompression were not excluded in this study (Table 2.1). Complications were recorded when a reoperation needed to be performed. Revision surgery by spinal fusion of the TDR was defined as a failure.

Clinical- and subjective outcome evaluation

Patient Reported Outcome Measures (PROMs) were obtained in all TDR patients who had not been revised at latest follow-up (n=237). Back- and leg-pain intensity was recorded with a Visual Analog Scale (VAS, 0 to 10, 10 being 'worst pain'). General well-being was evaluated using the Short Form-36 survey (SF-36) and Oswestry Disability Index (ODI). In both a score of 100 is equivalent to maximum disability and a score of 0 is equivalent to no disability. Quality of life was assed using the EuroQol-5D (EQ-5D, 0 to 1, 1 indicates the best health state).

The patient's subjective outcome evaluation was assessed by 3 questions. The first question was whether they were satisfied with the TDR operation. The second question was whether their current situation was better, the same, or worse in comparison to the first five-years after TDR. The third question was if they would choose the same surgery again.

Data analysis and statistics

Baseline patient characteristics were described using mean and standard deviation (SD) and absolute number and percentage. The independent samples t-test was used to test for differences in the means of the baseline patient characteristics between patients with- or without revision surgery by spinal fusion. Differences in categorical variables in the same groups were tested using the chi-square test.

Kaplan Meier curves were constructed to assess the cumulative incidence of fusion surgery after TDR over time. Multivariable Cox proportional hazards regression was used to estimate associations between patient characteristics and survival of the TDR. Corresponding hazard-ratios (HR) and 95% confidence intervals (CI) were obtained. A multivariable logistic regression model was utilized to identify independent risk factors associated with worse clinical outcome defined as a VAS-score for combined leg and back pain ≥5.0- or an ODI-score >40 points at latest follow-up. A cut-off p-value of ≤0.05 was considered statistically significant. All analyses were performed using IBM SPSS (Version 23.0).

Results

Study population

Altogether 405 consecutive patients with a TDR were identified. At follow-up, 34 patients had deceased (8.4%), 14 patients (3.4%) refused to participate, and 61 patients (15.1%) could not be traced. These 109 patients (26.9%) were excluded from further analysis. Informed consent was acquired from the remaining 296 patients (73.1%) with a mean follow-up of 19.4 years (median 19.3, range 0.2-25.6 years). A summary of the reasons for exclusion is listed in Figure 2.1.

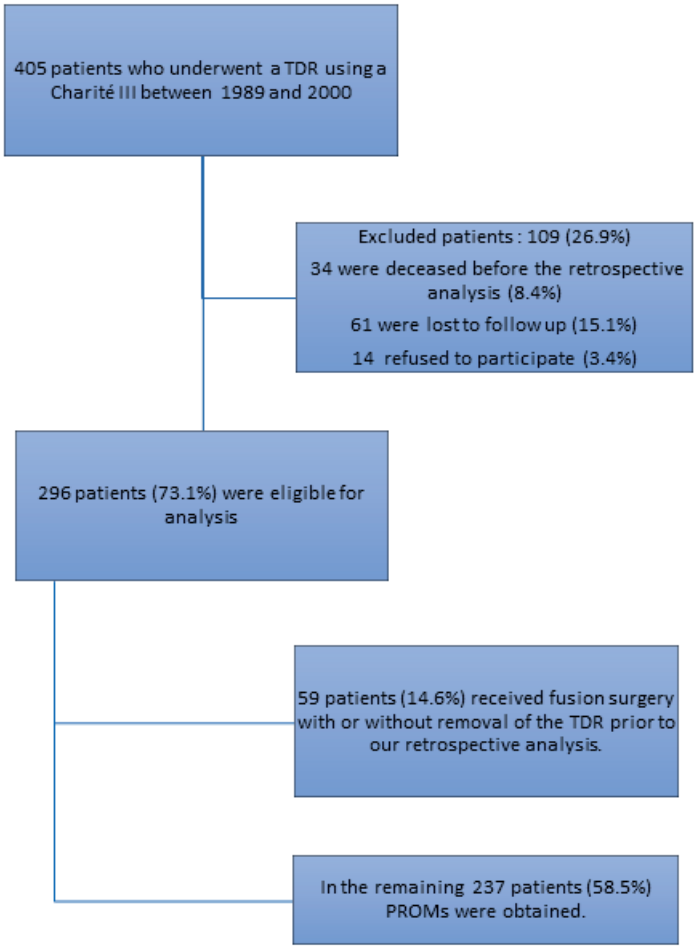

Figure 2.1 Reasons for exclusion.

In 59 patients (19.9%) a revision by spinal fusion with or without removal of the TDR had been performed at a mean of 7.1 years (median 6.7, range 0.2-21.6 years). The mean follow-up after implantation for the 237 patients (80.1%) without a revision was 19.5 years (median 19.1, range 13.7-25.6 years). Patient characteristics are listed in Table 2.1. Patients with a TDR at level L2-L3 or multilevel TDR had significantly more risk of needing to undergo revision fusion surgery (p=0.042 and p=0.011 respectively).

Table 2.1 Summary of subgroup patient demographic and surgical data.

	No revision	Revision	P - value[1]
N (%)	237 (80.1)	59 (19.9)	
Follow-up in years (range)	19.5 (13.7-25.6)	19.1 (7.6-26.3)	
Males, number (%)	102 (84.3)	19 (15.7)	0.130
Mean age at time of surgery, years (range)	41.9 (22.0-60.0)	40.6 (22.0-63.0)	0.227[2]
Surgical levels			
L2-L3 (%)	1 (33.3)	2 (66.7)	**0.042**
L3-L4 (%)	14 (73.7)	5 (26.3)	0.472
L4-L5 (%)	120 (77.9)	34 (22.1)	0.336
L5-S1 (%)	146 (79.8)	37 (20.2)	0.875
Number of levels (one: two: three)	193-44-0	43-14-2	**0.011**
Indication for lumbar disc replacement (n=261)			
DDD without any other accompanying pathologies (%)	160 (76.6)	49 (23.4)	0.221
DDD with a disc herniation and predominant axial low back pain (%)	21 (91.3)	2 (8.7)	
DDD following a discectomy (%)	24 (82.8)	5 (17.2)	

DDD=Degenerative Disc Disease. [1] Chi-square test; [2] independent t-test.

Survival analysis

A Kaplan Meier survival curve is depicted in Figure 2.2. The vast majority of the fusion procedures (n=48, 81.4%) occurred in the first 10-years after TDR.

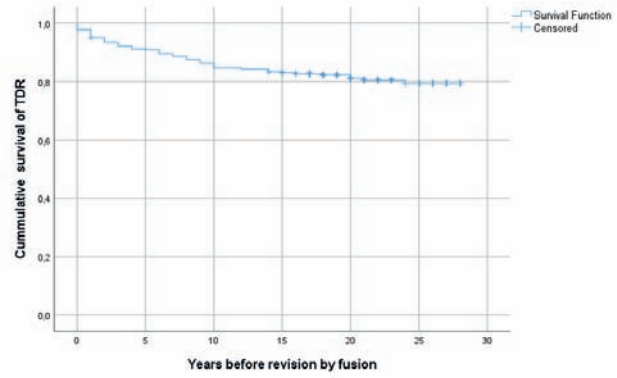

Figure 2.2 Kaplan Meier (survival of the TDR with fusion as endpoint n=59).

Reoperations

An overview of all complications requiring a reoperation is provided in Table 2.2. A total of 108 re-operations was performed in 92 patients, so the overall reoperation rate was 31.1%. Again, the majority occurred in the first 10 years after TDR (n=81, 88.2%). It was 29.5% for mono- (n=69) and 39.0% for the bi-segmental (n=23) TDRs (p=0.109). The mean time until reoperation was 4.0 years (range 0.0-21.6 years). These were divided into three subgroups: reoperations for immediate device- or technique related–complications (n=20, 6.8%), reoperations that were related to the surgery in general (n=7, 2.4%), and reoperations for the treatment of persisting symptoms (n=81, 27.4%).

Table 2.2 Different indications for a reoperation.

	N (% of total)	Mean time in months till complication (range)
Immediate device- or technique related–complications	20 (6.8)	12.87 (0.23-128.4)
Persistent leakage of liquor	1	
Anterior luxation TDR	13	
Malposition TDR	6	
Reoperations that were general surgery related	7 (2.4)	8.00 (0.03-18.4)
Deep surgical site infection	1	
Ileus requiring hemicolectomy	1	
Rectus hematoma	3	
Fascia defect	2	
Reoperations for the treatment of persisting symptoms	81 (27.4)	75.84 (0.16-258.8)
Radiculopathy or relative spinal stenosis	37	
Facet joint arthropathy	14	
Adjacent segment disease (cranial or caudal)	15	
Subsidence of the TDR	15	
Overall complication rate	92 (31.1%)	

In 34 patients (57.6%) a posterolateral instrumented fusion was performed. In 25 patients (42.4%) in addition to spinal fusion, the TDR was removed and the intervertebral defect was filled with a femoral head bone strut graft (Figure 2.3.). In all patients with complaints attributed to ASD, spinal fusion of the index- and affected adjacent segment was performed. The remaining 49 re-operations consisted of 8 procedures to resolve general complications such as a rectus hematoma or an incisional hernia of the abdominal wall. In 11 patients the TDR was repositioned after anterior luxation or malposition of the TDR. The remaining 30 procedures were related to radiculopathy or relative spinal stenosis as described by the surgeon. In these patients a decompression of the hypertrophied ligamentum flavum was performed, often in combination with a laminotomy and undercutting of the facet joints.

To investigate whether learning curve had an impact on reoperation rate, we looked at complications indicative for the latter. In the first 4 years (100 cases), anterior luxation of the TDR occurred 6 out the 13 cases (46.1%). For malposition this was 2 out of 6 cases (33.3%).

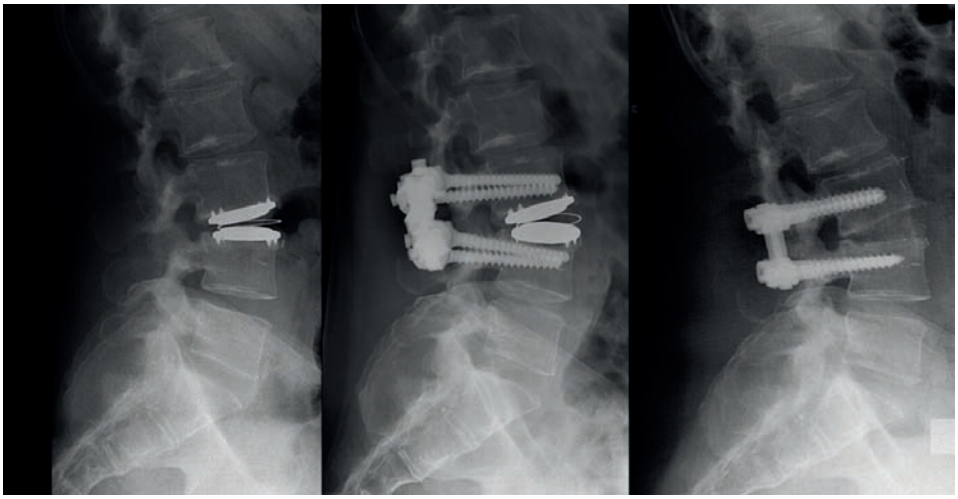

Figure 2.3 Example case before and after revision of the TDR by posterolateral instrumented spinal fusion and after second stage removal of the TDR, because of persisting complaints.

Risk factors for TDR survival and worse clinical outcome

An overview of all potential risk factors for revision surgery is provided in Table 2.3. A BMI>30 was associated with a significantly lower probability of revision surgery (HR 0.27, p=0.026). Although not statistically significant, previous spinal surgery (discectomy or small decompression) before TDR increased the probability of revision spinal fusion (HR=1.66, p=0.086). In contrast to the univariable analysis (Table 2.1), no significant differences were seen in the multivariable (adjusted) analysis for multilevel TDR or the level of placement. Therefore, they are not independent risk factors for failure. We tested for associations between all potential risk factors in relation to the different complications requiring a reoperation. A significant association was found for previous spinal surgery and ASD (occurrence of 4% vs. 14.3%, p=0.004).

An overview of all potential risk factors for a poor clinical outcome is provided in Table 2.4. Rheumatoid arthritis (RA) and age at the time of surgery < 45 years were both associated with a higher probability of a VAS≥5.0 (OR 5.08 and 1.95, respectively). Previous spinal surgery, osteoporosis (defined as taking medication for this condition, no data on bone mineral density was available), BMI>30, and RA were all associated with a higher probability of an ODI-score ≥40 (OR 2.19, 4.03, 2.40 and 7.15 respectively). The potential risk factors of a TDR at L2-L3 or L3-L4 were not included in this multivariable analysis because of too few events to estimate the OR.

When we define failure as a VAS≥5.0 and/or a revision operation (n=144, 48.6%), both RA (OR 5.01, p=0.014) and age at the time of surgery <45 years (OR 3.10, p=0,001) were associated with a higher probability of failure.

Table 2.3 Potential risk factors for revision surgery by spinal fusion.

	Revision surgery by spinal fusion					
	N	no	yes	Hazard ratio	Confidence Interval	P-value[1]
Total population	296	237 (80.1)	59 (19.9)			
≥Two levels	296	44 (73.3)	16 (26.7)	1.48	0.82-2.67	0.194
Level L2-L3 or L3-L4	296	15 (68.2)	7 (31.8)	1.81	0.82-3.99	0.144
Level L4-L5	296	120 (77.9)	34 (22.1)	1.19	0.71-2.01	0.509
Level L5-S1	296	146 (79.8)	37 (20.2)	1.09	0.64-1.86	0.760
Male gender	296	102 (84.3)	19 (15.7)	1.42	0.81-2.50	0.219
Age <45 years at time of surgery	296	159 (77.9)	45 (22.1)	1.53	0.85-2.76	0.156
Previous spinal surgery	283	40 (71.4)	16 (28.6)	1.66	0.93-2.30	0.086
Smoking	286	81 (81.8)	18 (18.2)	1.15	0.64-2.08	0.633
Rheumatoid arthritis	294	16 (76.2)	5 (23.8)	1.30	0.52-3.25	0.582
COPD	294	17 (81.0)	4 (19.0)	0.75	0.24-2.41	0.634
Osteoporosis[2]	293	15 (71.4)	6 (28.6)	1.79	0.76-4.17	0.181
BMI>30	289	48 (92.3)	4 (7.7)	0.27	0.08-0.86	0.026

[1]Cox multivariate regression; [2]Defined as taking medication for the treatment of osteoporosis.

Clinical- and subjective outcome evaluation

Analysis of the clinical parameters, at latest follow up, showed mean scores for: SF-36 physical of 39.9 (n=212, 12.1 SD), SF-36 mental of 50.9 (n=212, 11.2 SD), VAS-leg of 2.1 (n=235, 2.8 SD), VAS-back of 3.4 (n=235, 2.9 SD), ODI 26.7 (n=26.7, 18.7 SD), and for EQ5D of 0.737 (n=225, 0.232 SD).

In total, 79.6% of all patients (n=235) were satisfied with the outcome of their TDR at latest follow-up: 173 patients (73.0%) would be willing to undergo the same surgery again, 29 patients (12.2%) were not sure, and 33 patients (13.9%) would not be willing. When asked to compare their current situation with the first 5-years after surgery, 60 patients (25.3 %) reported a deteriorated clinical outcome.

Table 2.4 Overview of potential risk factors for a poor clinical outcome.

	VAS-score				ODI-score			
	N<5.0 (%)	N≥5.0 (%)	Odds ratio (CI)	P-value[1]	N<40 (%)	N≥40 (%)	Odds ratio (CI)	P-value[1]
Total population	161 (61.7)	100 (38.3)			155 (69.5)	68 (30.5)		
≥Two levels	29 (54.7)	24 (45.3)	1.08 (0.28-4.15)	0.909	29 (63.0)	17 (37.0)	1.20 (0.27-5.45)	0.813
Level L4-L5	76 (44.1)	76 (55.9)	1.48 (0.40-5.46)	0.557	80 (66.7)	40 (33.3)	1.26 (0.29- 5.50)	0.762
Level L5-S1	104 (64.2)	58 (35.8)	0.98 (0.28-3.42)	0.969	93 (69.9)	40 (30.1)	1.05 (0.25-4.33)	0.950
Male gender	71 (65.1)	38 (34.9)	1.19 (0.68-2.08)	0.552	73 (78.5)	20 (21.5)	1.84 (0.93-3.65)	0.079
Age <45 years at time of surgery	95 (57.2)	71 (42.8)	1.95 (1.06-3.56)	0.031	98 (69.5)	43 (30.5)	1.38 (0.69-2.77)	0.362
Previous spinal surgery	23 (48.9)	24 (51.1)	1.80 (0.90-3.62)	0.098	24 (55.8)	19 (44.2)	2.19 (1.02-4.72)	0.046
Smoking	48 (53.9)	41 (46.1)	1.55 (0.87-2.75)	0.135	42 (60.9)	27 (39.1)	1.95 (0.98-3.85)	0.056
Rheumatoid arthritis	6 (31.6)	13 (68.4)	5.08 (1.54-16.7)	0.008	5 (29.4)	12 (70.6)	7.15 (1.87-27.4)	0.004
COPD	9 (45.0)	11 (55.0)	1.67 (0.54-5.16)	0.370	9 (56.3)	7 (43.8)	0.72 (0.18-2.84)	0.722
Osteoporosis	8 (40.0)	12 (60.0)	1.20 (0.37- 3.89)	0.763	5 (31.3)	11 (68.8)	4.03 (1.01-16.0)	0.048
BMI >30	27 (54.0)	23 (46.0)	1.47 (0.75-2.87)	0.266	23 (56.1)	18 (43.9)	2.40 (1.10-5.26)	0.029

[1] Multivariable logistic regression; [2] Defined as taking medication for the treatment of osteoporosis.

Discussion

This study reports the long-term clinical follow-up of the Charité III lumbar TDR implanted by a single surgeon for the treatment of symptomatic DDD. In our study the overall reoperation rate was 31.1%. In 59 patients (19.9%) revision spinal fusion at the index level was performed. RA, osteoporosis, age at the time of surgery <45, BMI>30, and previous spinal surgery were all associated with a poor clinical outcome.

There is still much debate concerning the use of TDR in terms of fear of deteriorating effect and high rates of late revision operations.[15,18] To assess this issue the accumulation and analysis of long-term data are paramount. There are few studies with a minimal follow-up of 10-years.[11-14,16,17] They report a reoperation rate between 5-33 percent. Most of these studies have a mean follow-up around 11-years. In our study, with a mean follow-up of 19.4 years, the vast majority of reoperations, including revision spinal fusions, occurred in the first 10-years after TDR (88.2% and 81.4% respectively). It appears that there is no need for fear of late revision operations according to our data.

Our overall reoperation rate of 31.1% was similar to the rate of 33% in the study of Laugesen et al.[16] but higher in comparison to other long-term follow-up studies[11-14,16,17] reporting incidences between 5-9%. The mean follow-up in our study is higher in comparison to those studies[11-14,16,17], which may account for a relatively higher incidence of reoperations. Furthermore, this difference may have been caused by suboptimal patient selection for the index TDR surgery. In later years improvements have been made in terms of surgical technique, imaging of the spine, and more appropriate patient selection based on social profile.[11,15] This might explain the tendency of earlier studies, or those with longer follow-up, to report less favorable outcomes than those of more recent studies.[16] Learning curve does not seem to be a factor, since complications indicative for the latter, such as anterior luxation or malposition of the TDR are evenly distributed over the years.

TDR is associated with progression of facet joint arthropathy (FJA) at the index-level.[10] In our study, in 14 out of 59 patients (23.7%), FJA was reported as the reason for revision spinal fusion. However, it is likely that in patients classified as suffering from ASD, spinal stenosis, or subsidence; FJA has been a factor as well. This assumption is supported by the observation that in all patients (n=15) with revision spinal surgery for ASD, the index level was also fused.

A prospective study of Siepe et al.[15] with 181 patients and a mean follow-up of 7.4 years reported a reoperation rate of 16%. The incidence of either general surgery- or device-related complications in that study amounted to 7.2% and is quite similar to the 9.2% in the current study. It must be noted that in that study, as in the RCTs comparing TDR with

fusion[1-3], numerous exclusion criteria such as previous spinal surgery, obesity, and chronic steroid use, were applied. As that was not the case in the current study, our population might be a better representation of patients with DDD in daily clinical practice.

In addition, the reoperation rates should similarly be compared with the rates that have been published on lumbar fusions. A large retrospective cohort study in adults who underwent lumbar fusion for degenerative spine disorders between 1990 and 1993 (n=2345) showed a cumulative incidence of reoperations of 21.5% after 11-years follow-up.[20] This is similar to the revision fusion rate in our study but our overall reoperation rate is higher. However, when we look at our reoperation rate after 11 years follow-up (27.7%, n=82), the difference in reoperation rate is less pronounced.

Risk factors for survival and worse clinical outcome

A BMI >30 was associated with a significantly lower probability of revision surgery by spinal fusion (HR 0.27). It is possible that the surgeons were less inclined to perform revision surgery because of associated higher complication rates in the obese.[21] Moreover it is possible that these obese patients had a lower activity resulting in less wear of the TDR, as has been published for obese patients with hip- and total knee replacements.[22] The fact that in our population BMI>30 was associated with an ODI-score >40 might be indicative of the latter. However not statistically significant (p=0.086), previous spinal surgery before TDR tended to increase the probability of revision spinal fusion (HR=1.66) in our population.

In contrast to the study of Siepe et al.[15] multilevel TDR did not significantly increase the probability of revision surgery or poor clinical outcome in our multivariable analysis. These findings are consistent with several other studies.[16,19,23] The level of TDR was not associated with an increase in revision surgery or a decrease in clinical outcome as well. This again is consistent with the literature.[24,25] Rheumatoid arthritis, osteoporosis, age at the time of surgery <45 and previous spinal surgery were all associated with a VAS-score ≥5.0 or an ODI-score ≥40. Tropiano et al. showed similar results for age and previous spinal surgery.[19]

Clinical- and subjective outcome evaluation

PROMs were obtained at latest follow-up in all patients without a previous revision by spinal fusion. This means that these outcome measurements are not a reflection of our total population. Furthermore, no preoperative questionnaires were available for comparison. However, it is possible to compare our outcome measurement with those reported in the other mid-to long-term follow-up studies on TDR.

Siepe[15], Lu[13], and Park et al.[17] reported at latest follow-up an ODI-score of 20.3, 13.2, and 22.4 and a VAS-score of 3.3, 1.5, and 3.4 respectively. These numbers are comparable to those in our study (VAS-score of 3.4, ODI-score of 26.7) although it must be noted that in these three studies patients with a revision by spinal fusion were included (11%, 6.3%, and 9.3% respectively). Laugesen et al.[16] reported a VAS-score of 2.4 and a SF-36 physical of 31.9 in their group without a revision, both similar to our population (SF-36 physical of 39.9)

In our study 79.6% of the patients were satisfied with their TDR and 73.0% would be willing to undergo the same surgery again for similar complaints. When assuming that all patients with a fusion were not satisfied and not willing, these percentages would drop to 63.6% and 58.16% respectively. Previously mentioned studies reported percentages between 86.3%-64.9% and 79.3%-52.6% respectively.[13,15-17] To our opinion the clinical status of patients after TDR at a follow-up of almost 20-years is not substantially different from those at 8-12-years follow-up.[13,15-17]

Limitations and strengths

The current study's main limitation is its retrospective nature. PROMs were obtained at latest follow-up and no preoperative questionnaires were available for comparison. Unfortunately, most of the other long-term follow-up studies had a retrospective design.[11,12,14,17] A lack of control group (either nonoperative or index spinal fusion) can be attributed to all these studies.

The number of patients included in any study has a vital influence on the outcome and whether a study is representative or not. We included a total of 296 patients. Our mean follow-up of 19.4 years is the longest available in the literature. Despite our long follow-up, only 18.5% of our patients were lost to follow-up or refused to participate. Consequently, there is a high chance of generalizability of our study.

The results presented in this study demonstrate a revision spinal fusion rate of 19.9% after a mean follow-up of 19.4 years. Fear of excessive late complications or reoperations following the primary TDR cannot be substantiated since the vast majority of all reoperations occurred in the first 10 years after TDR. Proper patient selection considering the identified risk factors for worse outcome may help to improve the clinical and functional outcome in these patients.

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Long-term residual-mobility and adjacent segment disease after total lumbar disc replacement

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Abstract

Study design
Retrospective cohort study

Objectives
Total disc replacement (TDR) has been introduced in order to preserve segmental motion and thus reduce Adjacent Segment Disease (ASD) as seen after spinal fusion. However, it is uncertain whether these presumed beneficial effects remain. The aim of this study was to evaluate the long-term incidence of ASD and residual-mobility in relation to clinical outcome.

Methods
Two hundred and ten patients treated with lumbar TDR for degenerative disc disease were invited for follow-up. ASD was reported in case of severe degeneration in an adjacent disc at latest follow-up, or if an increase in disc degeneration was observed in these adjacent segments as compared to direct post-operative radiographs. Residual-mobility of the TDR was defined as a minimal rotation of 4.6° on flexion-extension radiographs. Patient Reported Outcome Measures were obtained.

Results
Fifty seven patients (27.1%) were lost to follow-up. In 32 patients (15.3%) a revision by spinal fusion had been performed. In 20 patients this revision had occurred ≥5 years after TDR and were included. Consequently 141 patients were available for analysis (mean follow-up of 16.7 years). Residual-mobility was noted in 38.0%. No significant associations were observed between residual-mobility and the occurrence of ASD or with clinical outcome. In addition, ASD and clinical outcome were not related either.

Conclusions
It appears that long-term preservation of motion after TDR is met for only a third of patients. However, residual-mobility is not associated with the occurrence of ASD, and both residual-mobility and ASD do not appear to be related to long-term clinical outcome.

Introduction

Fusion of a symptomatic lumbar spinal motion segment is the most commonly used operative treatment for patients with degenerative disc disease (DDD), unresponsive to non-operative care.[1] Total Disc Replacement (TDR) has been introduced in order to preserve motion at the affected level and mimic the morphology of the intervertebral disc,[2,3] aiming to prevent the occurrence of adjacent segment disease (ASD) as seen after lumbar fusion, and thus a presumably better long-term outcome.[4-7]

The predicted reoperation rate of ASD after spinal fusion ranges between 9.9% and 22.2% at 10 year follow-up.[4,6,7] Studies reporting on the incidence of ASD after TDR with a minimal follow-up of at least 10 years are scarce. Those available report an incidence of ASD as determined on plain radiographs of the lumbar spine between 2% and 17% at mean follow-up of 10 to 17.3 years.[8-10] A systematic review by Wang et al.[11] showed a pooled risk of clinical ASD that needed revision surgery of 1.2% and 7.0% in the TDR and fusion groups respectively, after maximum of 5 years follow-up. A randomized controlled trial of Zigler et al.[12], comparing TDR with lumbar fusion, indicated that TDR has a protective effect against ASD, five years after the index surgery.

Multiple studies with a follow-up of 2 to 11 years, have shown that range of motion (ROM) was preserved or even improved after TDR.[9,10,13,14] None of these studies evaluated residual-mobility in relation to the occurrence of ASD and clinical outcomes.

The purpose of this study was to evaluate residual-mobility and the long-term incidence of ASD after TDR. Additionally, an assessment was made whether ASD and residual-mobility were related to clinical outcome.

Methods

Patient selection

The current study was approved by the medical ethics committee METC-Z (16-N-22) and registered at the Dutch Trial Registry (NTR5710). The medical records of all patients who received a lumbar TDR using an SB Charité III between 1994 and 2000 at the Zuyderland Medical Centre, Sittard, The Netherlands, were reviewed.

TDR had been performed for the treatment of patients with lumbar DDD causing predominant axial low back pain. Nerve root compression and/or spinal stenosis was considered as a contraindication for TDR. Preoperatively, all patients had undergone

fluoroscopically guided provocation discography to confirm a painful disc. No facet joint injections were performed. Patient characteristics are listed in Table 3.1.

Table 3.1 Summary of subgroup patient demographic and surgical data.

	Patients (n=141)
Males, number (%)	63 (44.7)
Mean age at time of surgery, years (SD)	42.3 (7.3)
Previous spinal surgery (%)	24 (17.0)
Mean Body Mass Index at time of surgery (SD)	26.9 (4.1)
Surgical levels	
L2-L3 (%)	1 (0.8))
L3-L4 (%)	3 (2.5)
L4-L5 (%)	58 (48.0)
L5-S1 (%)	74 (61.1)
Number of levels (one level: two levels)	123:18
Indication for lumbar disc replacement (n=137)	
DDD[1] without any other accompanying pathologies (%)	101 (73.7)
DDD[1] with a disc herniation and predominant axial low back pain (%)	21 (15.3)
DDD[1] following a discectomy (%)	15 (10.9)

[1] Degenerative disc disease.

Radiological analysis

The radiographic grading-system of Wilke[15] was used to determine the degree of intervertebral disc degeneration (Figure 3.1). This grading-system covers three radiographic signs of disc degeneration: 'Height Loss', 'Osteophyte Formation', and 'Diffuse Sclerosis'. On standing antero-posterior and lateral radiographs these three variables were graded individually on a scale from 0 to 3. Based on the sum of these three scores, the overall degree of degeneration was assigned to each disc on a four-point scale from grade-0 (no degeneration, 0 points) to grade-3 (severe degeneration, 7-9 points).[15]

Patients were considered to have developed ASD, if in one or more adjacent segments of the TDR a grade-3 disc degeneration was observed at latest follow-up (ASD-static). We confirmed that this grade-3 disc degeneration was not already present in the same segment at the direct post-operative radiographs. We also considered ASD to be present if an increase of 3 or more points was observed in the same adjacent segment when the direct post-operative radiographs were compared with those at latest follow-up (ASD-dynamic).

Radiographic grading system for lumbar intervertebral disc degeneration (based on lateral and postero-anterior radiographs)			
Height loss	Psteophyte formation	Diffuse sclerosis	Overall degree of degeneration
Anterior and posterior height loss with respect to the individual height before degeneration	Sum of points of eight edges No osteophytes: 0 points <3 mm: 1 point ≥3 mm but <6 mm: 2 points ≥6 mm 3 points	Sum of points of both adjacent vertebral Bodies No sclerosis: 0 points 0.25 partially or completely affected: 1 point 0.5 partially or completely affected: 2 points >0.5 partially or completely affected: 3 points	Sum of points of "Heiht Loss", "Osteophyre Formation" and "Diffuse Sclerosis"
0 = 0% 1 = <33% 2 = ≥33 but <66% 3 = ≥66%	0 = 0 points 1 = 1-8 points 2 = 9-16 points 3 = 17-24 points	0 = 0 points 1 = 1-2 points 2 = 3-4 points 3 = 5-6 points	0 points = grade 0 (no degeneration) 1-3 points = grade 1 (mild degeneration) 4-6 point = grade 2 (moderate degeneration) 7-9 points = grade 3 (severe degeneration)
The three variables "Height Loss", "Osteophyte Formation" and "Diffuse Sclerosis" are first graded individually on a sclae from 0 to 3. The "Overalla Degree of Degeneration"is then assigned according to the sum of these three scores.			

Figure 3.1 Radiographis grading-system by Wilke et al.[15] to determine the degree of intervertebral disc degeneration.

The Cobb method was used to calculate the sagittal alignment angles of the TDR in the flexion- and extension radiographs.[16] A kyphotic angle was assigned a negative value, lordosis a positive value. According to a study by Lim et al, it appears that in order to be sure with 95% certainty that a TDR has any sagittal motion, a range of motion (ROM) of at least 4.6° should be observed on standard flexion-extension lumbar spine radiographs.[16] Consequently, residual-mobility was defined as a minimal change of 4.6° in the sagittal alignment angles. We used the method of Punt et al.[17] to quantify radiological subsidence in the current population. Finally, the pelvic incidence (PI) was measured on the lateral radiographs. All measurements were performed by two independent observers, who were not involved in patient care (JK, TV). Mean values of their measurements were calculated. The interclass correlation coefficient was used to quantify agreement between the two observers.

Clinical outcome evaluation

Patient Reported Outcome Measures (PROMs) were obtained from all patients at their follow-up visit to the outpatient clinic. Back- and leg-pain intensity was recorded with a Visual Analog Scale (VAS, 0 to 100, 100 being 'worst pain'). General and functional well-being was evaluated using the Short Form-36 survey (SF-36) and Oswestry Disability Index (ODI), respectively. In both a score of 0 is equivalent to no disability and a score of 100 is equivalent to maximum disability. Quality of life was assessed using the EuroQol-5D (EQ-5D, 0 to 1, 1 indicates the best health state). Finally, patients were assigned to a success- or failure-group: a revision by spinal fusion or a reported VAS pain-score ≥50 was classified as failure.[18]

Data analysis and statistics

Baseline patient characteristics were described using mean and standard deviation or absolute number and percentage. The independent t-test was used to test for differences in the means of radiological parameters and clinical outcome scores between patients with- or without residual-mobility or ASD. Differences in categorical variables in the same groups were tested using the chi-square test. A multivariable logistic regression model was utilized to identify if there is an independent association between the occurrence of residual-mobility and ASD. Confounding variables that were used for the multivariable analysis are those listed in Table 3.1. Confounding variables were determined a priori, not by means of statistical testing. Corresponding estimates of adjusted odds-ratios (OR) and 95% confidence intervals (CI) were obtained. A p-value of <0.05 was considered statistically significant. All analyses were performed using IBM SPSS (Version 23.0).

Results

Study population

Altogether 226 patients with a TDR were identified, 16 patients had deceased (7.1%). The remaining 210 patients were contacted by mail and subsequently by phone, with the request to visit our outpatient clinic. A total of 57 patients (27.1%) could not be retrieved. In 32 patients a revision by spinal fusion had been performed prior to our study. We only included patients if the revision had occurred at least five years after the initial TDR, to be able to report on changes in the adjacent levels at long-term follow-up (n=20, range 5-22 years). Consequently, 141 patients (67.1%) were included for analysis. Informed consent was acquired in all patients. A flowchart of the in- and excluded patients is shown in Figure 3.2.

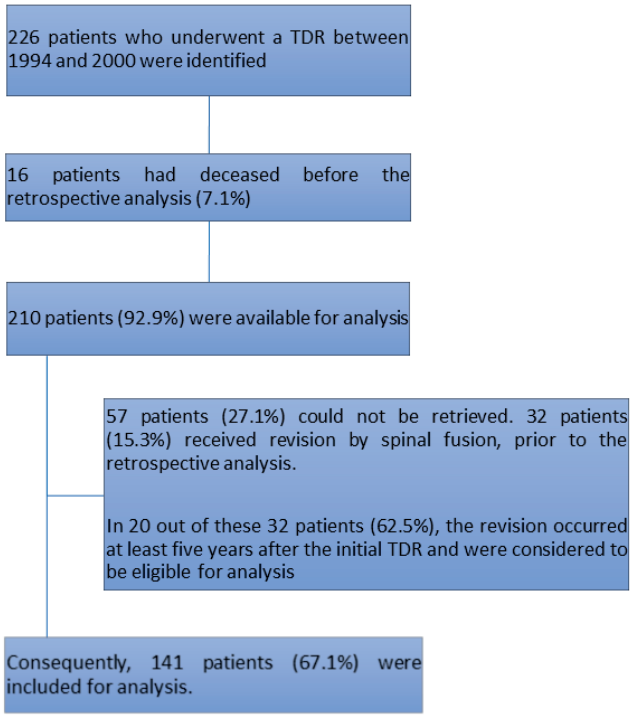

Figure 3.2 Reasons for exclusion.

Mean follow-up after implantation for the 121 TDR patients without revision fusion was 16.7 years (median 16.5, range 13.6-23.0 years). In 15 patients a TDR had been placed at two or more levels. In 18 out of the 121 patients without a revision, the direct post-operative radiographs were not available. In 12 out of the 20 patients with a revision,

either the direct post-operative- or the radiographs before spinal fusion were not available. Consequently, in 111 patients the development of ASD after TDR could be determined.

Incidence of residual-mobility and ASD

As shown in Table 3.2, only 46 out of 121 TDR patients (38.0%) had a residual-mobility of ≥4.6° at latest follow-up. The mean ROM in the present study was 4.3° (range: 0°-15.6°). High interclass correlation coefficients between the two observers were found (R≥0.899, p<0.01). In 55 patients a grade-3 disc degeneration (7-9 points) was scored in one or both the adjacent levels at latest follow-up. In 4 patients this degeneration was already present, in the same adjacent level on the direct post-operative radiographs. Consequently, ASD-static occurred in 51 out of 107 patients (47.7%, one level n=38, both levels n=13). As to ASD-dynamic, in 28 out of the 111 patients (25.2%) an increase of 3 or more points in one (n=14) or both (n=14) of the same adjacent segments was observed. No significant differences were seen for the occurrence of residual-mobility and ASD when the results were corrected for mono- versus bi-segmental TDR.

Table 3.2 Patient characteristics in relation to residual-mobility.

		Residual-mobility (>4.6° of motion)		
	N[1]	No	Yes	P-value[2]
N (percentage)	**121**	**75 (62.0)**	**46 (38.0)**	
Two or more levels (%)	121	9 (60.0)	6 (40.0)	0.866
Level L2-L3 (%)	121	1 (100.0)	0 (0.0%)	0.432
Level L3-L4 (%)	121	1 (33.3)	2 (66.7)	0.301
Level L4-L5 (%)	121	37 (62.7)	22 (37.3)	0.872
Level L5-S1 (%)	121	45 (61.6)	28 (38.4)	0.924
Body Mass Index >30 (%)	121	13 (59.1)	9 (40.9)	0.783
Age <45 years (%)	121	31 (60.8)	20 (39.2)	0.817
Pelvic incidence, mean (SD)	121	54.0 (13.6)	52.6 (12.1)	0.581[3]
Pelvic incidence >65° (%)	121	13 (68.4)	6 (27.8)	0.529
Radiological subsidence (%)	121	33 (61.1)	21 (38.9)	0.822
ASD grade 3 at latest follow-up (%)	99	27 (60.0)	18 (40.0)	0.622
ASD increase of 3 or more points (%)	103	13 (50.0)	13 (50.0)	0.140
VAS total, mean (SD)	118	39.2 (28.4)	39.9 (29.1)	0.896[3]
VAS total > 50 (%)	118	26 (60.5)	17 (39.5)	0.813
RAND-36 physical, mean (SD)	114	40.4 (11.7)	37.6 (9.5)	0.178[3]
RAND-36 mental, mean (SD)	114	51.7 (11.9)	49.3 (12.1)	0.309[3]
ODI, mean (SD)	111	27.8 (17.3)	29.2 (16.7)	0.674[3]
ODI <40 (%)	111	52 (65.0)	28 (35.0)	0.497
EQ5D, mean (SD)	115	0.743 (0.186)	0.715 (0.235)	0.486[3]

[1] Total number of patients eligible for analysis; [2] Chi-square test; [3] Independent t-test.

Residual-mobility versus patient characteristics, ASD and clinical outcome

No significant associations were found between the different patient- or procedure-related characteristics such as the level of placement or multilevel TDR, and the

occurrence of residual-mobility (Table 3.2). Additionally, no significant associations were found for the VAS-, SF-36-, EQ5D-, or ODI-score and the occurrence of residual-mobility. Finally, no significant changes were observed when the occurrence of residual-mobility and those of ASD-static or ASD-dynamic were compared. The latter was confirmed in a multivariable logistic regression analysis, with an OR of 0.85 (CI 0.34-2.08, p=0.713) for ASD-static and 0.46 (CI 0.17-1.21, p=0.113) for ASD-dynamic (Table 3.3). All potential confounders were included in the analysis, besides a TDR at L2-L3 or L3-L4 because of too few events to estimate the OR.

Table 3.3 Multivariable logistic regression model between the occurrence of residual-mobility and ASD with potential confounders.

	Odds ratio	Confidence interval	P-value[1]
ASD grade-3 at latest follow-up (ASD-static)	0.85	0.34 - 2.08	0.713
ASD increase of 3 or more points (ASD-dynamic)	0.46	0.17 - 1.21	0.114
Male Gender	1.32	0.54 - 3.20	0.542
Previous Spinal surgery	2.34	0.67 - 8.10	0.181
TDR on two levels	0.81	0.08 - 7.53	0.812
Level L4-L5	2.19	0.19 - 25.72	0.534
Level L5-S1	2.85	0.26 - 31.76	0.394
Body Mass Index >30	1.42	0.46 - 4.43	0.541
Age <45 years	0.66	0.27 - 1.64	0.369
Diagnosis of DDD[2] without other pathologies	0.90	0.32 - 2.49	0.837

[1] Multivariable logistic regression; [2] Degenerative disc disease.

As previously mentioned, a sagittal motion of at least 4.6° should be observed, in order to be sure with 95% certainty that a TDR has any ROM. However, this does not exclude motion in those patients who do not meet this threshold. If we look more closely to these patients, their median sagittal motion is 2.2°. If this value is applied as a cut-off for ankylosis, 50.3% of the patients without residual-mobility may have some degree of motion. Therefore, we adjusted the threshold for residual-mobility (4.6°) in steps of 0.5° from 0 to the maximum measured sagittal ROM, to test if this affected our results. Similarly, no significant associations were observed between the different thresholds for residual-mobility and the occurrence of ASD or clinical outcome.

ASD versus patient characteristics, pelvic incidence and clinical outcomes

As for residual-mobility, we found no significant associations between the different patient- or procedure-related characteristics and the occurrence of ASD-static or ASD-dynamic (Table 3.4). Remarkably, in all 4 TDRs that were placed at a level cranial of L4-L5, ASD-static was observed (n=4, p=0.025). Pelvic incidence was not significantly associated with the occurrence of ASD. No significant associations were found for the VAS-, SF-36-, EQ5D-, or ODI-score and the occurrence of ASD-static or ASD-dynamic (Table 3.4). Finally, no significant differences were found between the success- and failure group for the occurrence of ASD-static or ASD-dynamic (Table 3.5).

Table 3.4 Patient characteristics in relation to ASD.

	ASD grade-3 at latest follow-up				ASD increase of 3 or more points			
	N[1]	no	yes	P-value[2]	N	no	yes	P-value[2]
N (percentage)	**107**	**56 (52.3)**	**51 (47.7)**		**111**	**83 (74.8)**	**28 (25.2)**	
TDR on two levels (%)	107	4 (30.8)	9 (69.2)	0.097	111	11 (78.6)	3 (21.4)	0.726
Level L2-L3 (%)	107	0 (0.0)	1 (100.0)	0.292	111	1 (100.0)	0 (0.0)	0.560
Level L3-L4 (%)	107	0 (0.0)	3 (100.0)	0.066	111	2 (66.7)	1 (33.3)	0.743
Level L4-L5 (%)	107	26 (50.0)	26 (50.0)	0.638	111	42 (76.4)	13 (23.6)	0.702
Level L5-S1 (%)	107	34 (53.1)	30 (46.9)	0.842	111	49 (74.2)	17 (25.8)	0.876
Body Mass Index >30 (%)	107	11 (57.9)	8 (42.1)	0.625	111	17 (85.0)	3 (15.0)	0.273
Age <45 years (%)	107	21 (46.7)	24 (53.3)	0.317	111	37 (77.1)	11 (22.9)	0.625
Pelvic incidence, mean (SD)	106	55.6 (14.9)	50.8 (12.0)	0.076[3]	110	54.4 (13.9)	51.01 (13.5)	0.280[3]
Pelvic incidence >65° (%)	106	13 (72.2)	5 (27.8)	0.172	110	15 (78.9)	4 (21.1)	0.679
VAS total, mean (SD)	97	42.3 (29.1)	36.0 (28.9)	0.294[3]	101	40.9 (28.9)	32.6 (28.1)	0.216[3]
VAS total >50 (%)	97	20 (55.6)	16 (44.4)	0.889	101	28 (75.7)	9 (24.3)	0.940
RAND-36 physical, mean (SD)	94	38.4 (10.9)	39.9 (11.1)	0.532[3]	94	39.1 (11.1)	40.4 (10.1)	0.642[3]
RAND-36 mental, mean (SD)	95	50.4 (12.6)	52.5 (11.2)	0.692[3]	99	50.3 (12.5)	53.3 (8.6)	0.285[3]
ODI, mean (SD)	91	28.9 (16.8)	27.6 (17.4)	0.975[3]	95	28.9 (17.5)	26.1 (15.5)	0.667[3]
ODI <40 (%)	91	37 (57.8)	27 (42.2)	0.601	95	53 (77.9)	15 (68.2)	0.687
EQ5D, mean (SD)	94	0.744 (0.200)	0.707 (0.225)	0.400[3]	98	0.727 (0.223)	0.750 (0.155)	0.650[3]

[1] Total number of patients eligible for analysis; [2] Chi-square test; [3] Independent t-test.

Table 3.5 Patient characteristics and the occurrence of ASD in relation to the success- and failure group.

	N[1]	Success-group	Failure-group	P-value[2]
N (percentage)	**141**	**83 (58.9)**	**58 (41.1)**	
TDR on two levels (%)	141	12 (66.7)	6 (33.3)	0.471
Level L2-L3 (%)	141	1 (50.0)	1 (50.0)	0.797
Level L3-L4 (%)	141	1 (33.3)	2 (66.7)	0.364
Level L4-L5 (%)	141	37 (54.4)	31 (45.6)	0.300
Level L5-S1 (%)	141	56 (64.4)	31 (35.6)	0.092
Body Mass Index >30 (%)	141	16 (72.7	6 (27.3)	0.240
Age <45 years (%)	141	42 (60.0)	28 (19.6)	0.170
Pelvic incidence, mean (SD)	129	51.9 (12.5)	56.7 (13.9)	0.058[3]
Pelvic incidence >65° (%)	129	12 (57.1)	9 (42.9)	0.419
ASD grade 3 at latest follow-up (%)	107	30 (58.8)	21 (41.2)	0.439
ASD increase of 3 or more points (%)	111	18 (64.3)	10 (35.7)	0.967

[1] Total number of patients eligible for analysis; [2] Chi-square test; [3] Independent t-test.

Discussion

This study represents a long-term follow-up of patients who received a lumbar TDR for the treatment of symptomatic DDD. Residual-mobility was noted in one third of our patients at latest follow-up. No significant associations were observed between residual-mobility and the different patient- or procedure-related characteristics, clinical outcome, or the occurrence of ASD. We found no significant associations between ASD and clinical outcome.

Incidence of residual-mobility and ASD

The number of long-term follow-up studies addressing the occurrence of residual-mobility after TDR is limited.[9,10,13,14] These studies reported a mean ROM between 7.7° and 10.3° at latest follow-up (mean 10-12 years). However, none of these studies defined residual-mobility. In the present study residual-mobility (ROM>4.6°) at the index level of the TDR was found in only 38.0% of the patients (n=46). The mean ROM was 4.3° which is slightly lower than in the other studies, but may be explained by the fact that our follow-up duration was longer. In studies where ROM was monitored over time, a gradual decline of the device mobility was noted.[14,19] This however, did not negatively impact the patient's clinical outcomes in these studies. In the current study, the ROM was only available at latest follow-up.

Studies with long-term follow-up of lumbar TDR (mean 10 to 17.3 years) report an incidence of ASD-static as determined on plain radiographs between 2% and 17%.[8-10] A prospective study by Meir et al.[20] with a mean follow-up of 9 years (range 8-11 years) reported an incidence of ASD-static on MRI of 68%. Based on plain radiographs we found

an incidence of ASD-static of 47.7%, which seems consistent with the study of Meir, although not with the other studies. This could possibly be explained by the fact that these studies did not use a standardized scoring-system for ASD. We used the grading-system of Wilke et al.[15], who compared the radiographic-scoring of DDD with the macroscopic grade of DDD and reported a Kappa-value of 0.713. Furthermore, the incidence of radiographic-ASD seems to increase when long-term studies[8-10,20] are compared with short-term studies.[12,21] However, this could also be part of the natural aging process. Two studies by Zigler et al. showed that the risk of dynamic-ASD following TDR is significantly lower when compared with spinal fusion at five years follow-up.[12,21] However, the appearance of ASD does not seem to significantly increase revision surgery or deteriorate clinical outcome in these studies.[12,21]

Residual-mobility versus patient characteristics, ASD and clinical outcomes

In the present study the different patient- or procedure-related characteristics did not have any influence on the occurrence of residual-mobility. To our knowledge only the retrospective study of Huang et al.[22] reported an association between residual-mobility and clinical outcomes. In that study (n=32) patients with a residual-mobility of >5° had clinically modest but statistically significant lower ODI-scores after a mean follow-up of 8.7 years. Our results showed no significant relationship between the occurrence of residual-mobility and the occurrence of ASD. This is similar to the results reported in the prospective study of Siepe et al.[23] (n=91) and an RCT by Zigler et al.[12] (n=261), both with 4 to 5 years of mean follow-up.

Biomechanical studies have shown that the movement of a TDR differs from that of a normal disc in an intact spine.[24,25] These studies described an increase in rotational mobility at the index TDR level. Furthermore, in a study of Nunley et al.[26] pressure effects on adjacent level discs after 2-level constructs, i.e., fusion, hybrid, and TDR were compared. No significant differences were found between the different stabilization procedures. So maybe not so much the extent of motion (in degrees), but rather the quality of motion is the main factor in the occurrence of ASD.

Other biomechanical studies have demonstrated increased facet pressure and altered loading patterns with more sudden, rather than gradual load increase in the facet joints after TDR.[27,28] It is not possible to make a reliable assessment of FJD on plain radiographs. Therefore, we could not investigate a possible association between FJD and the occurrence of residual-mobility or clinical outcome. Siepe et al.[23] reported a significant increase of facet joint degeneration (FJD) at the index level after TDR and a significant decrease in ROM at the same level. The occurrence of FJD was associated with significantly lower VAS- and ODI-scores. This may explain why in our study, as in many other studies,[12,21,23] no significant associations were found between ASD and

clinical outcome. FJD might be a stronger factor influencing clinical outcomes after TDR than ASD.

Study limitations and strengths

The current study's main limitation is its retrospective nature. We were only able to report on the changes in residual-mobility and ASD between directly post-operative and at latest follow-up. TDR has been introduced in order to preserve motion and thus prevent or decrease the occurrence of ASD as seen after lumbar spinal fusion.[4-7] Our study lacks a control group so evidently no direct comparison between TDR and fusion or between TDR and conservative treatment regarding the occurrence of ASD could be made.

We are aware that the radiographic measurements of residual-mobility are prone to error and a cut-off value of 4.6 degrees may seem arbitrary.[16] However a sensitivity analysis with different cut-off values led to the same results. To determine the degree of intervertebral disc degeneration, the standardized and validated radiographic grading-system of Wilke et al.[15] was used in order to obtain reproducible and accurate values.

We included 141 patients, which is more than in previously published long-term follow-up studies reporting on ASD or residual-mobility after TDR.[3,9,10,14] Our mean follow-up of 16.7 years is the longest available in the current literature on this subject and this might explain the substantial number of patients who were lost to follow-up, mainly due to patients who had died or could not be retrieved.

Conclusions

It appears that the initial goal of TDR, i.e., long-term preservation of motion, is met for only one third of our patients. Residual-mobility is not associated with the occurrence of ASD. Both residual-mobility and ASD seem unrelated to long-term clinical outcome.

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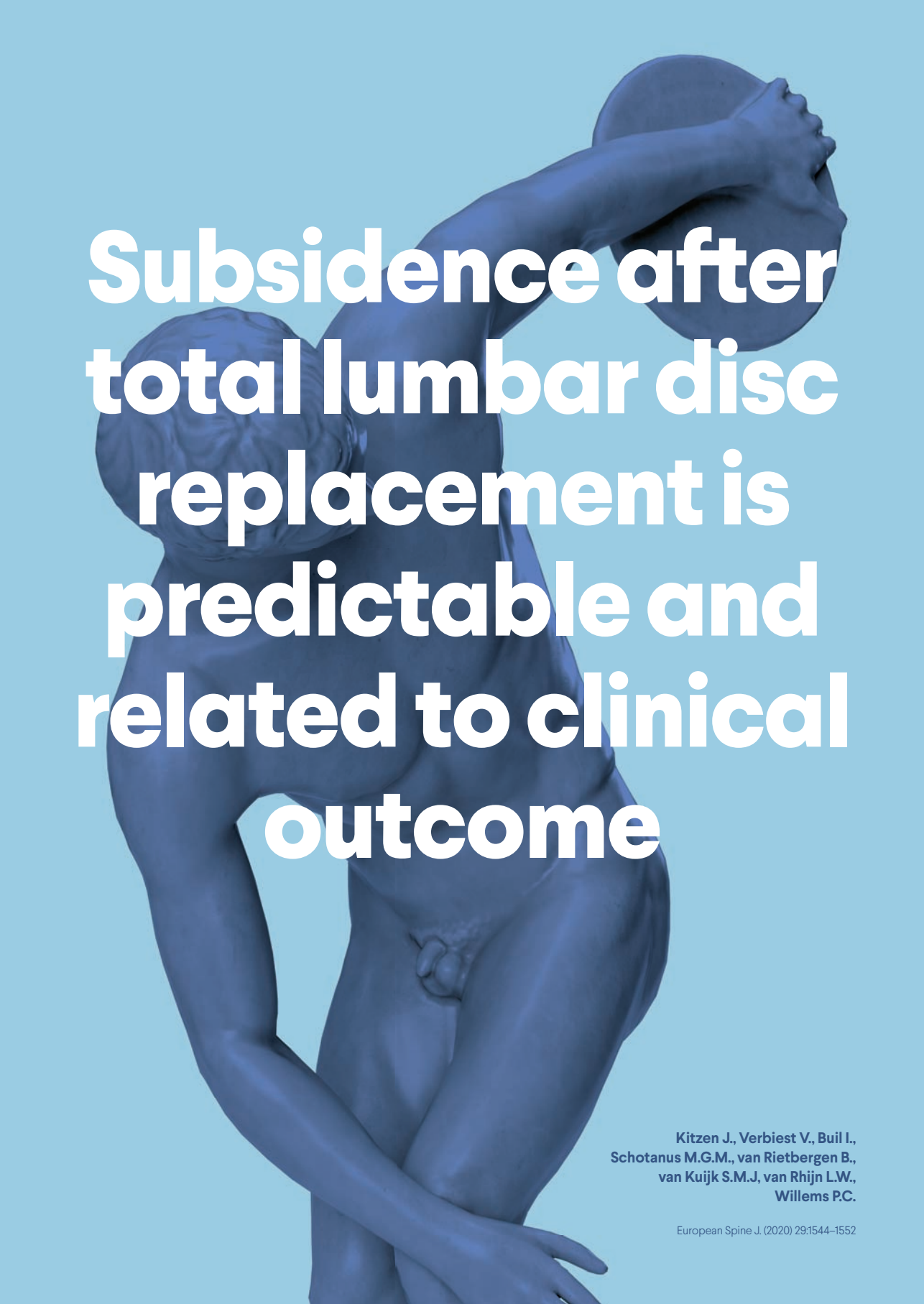

Subsidence after total lumbar disc replacement is predictable and related to clinical outcome

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Abstract

Purpose

As yet, there are no studies describing a relationship between radiographic-subsidence after lumbar total disc replacement (TDR) and patient symptoms. To investigate if subsidence, in terms of Penetrated Bone Volume or Angular Rotation over time (ΔPBV and ΔAR), is related to clinical outcome. To assess if subsidence can be predicted by position (Implant Asymmetry, IA) or relative size of the TDR (Areal Undersizing Index, AUI) on direct-postoperative radiographs.

Methods

Retrospective cohort study of 209 consecutive patients with lumbar TDR for degenerative disc disease. A 3-dimensional graphical representation of the implant in relation to the bony endplates was created on conventional radiographs. Consequently, the PBV, AR, IA and AUI were calculated, direct-postoperative (DPO) and at last follow-up (LFU). For clinical evaluation patients with substantial pain (VAS≥50) and malfunction (ODI≥40) were considered failures.

Results

At a mean follow-up of 16.7 years, 152 patients (73%) were available for analysis. In 32 patients revision by spinal fusion had been performed. Both ΔAR (4.33° vs. 1.83°, p=0.019) and ΔPBV (1448.4 mm^3 vs. 747.3 mm^3, p=0.003) were significantly higher in the failure- compared to the success-group. Using ROC-curves, thresholds for symptomatic-subsidence were defined as ΔPBV ≥829 mm^3 or PBV-LFU ≥1223 mm^3 (Area Under the Curve (AUC) 0.723, p=0.003 and 0.724, p=0.005, respectively). Associations between symptomatic subsidence and AUI-DPO≥0.50 (AUC 0.750, p=0.002) and AR-DPO≥3.95° (AUC 0.690, p=0.022) were found.

Conclusion

Subsidence of a TDR is associated with a worse clinical outcome. The occurrence of subsidence is higher in case of incorrect placement or shape mismatch.

Introduction

Fusion of a symptomatic lumbar spinal motion segment is the most commonly used operative treatment for patients with degenerative disc disease (DDD) not responding to conservative care.[1] However, spinal fusion is associated with negative side effects such as proximal facet-joint violation, pseudarthrosis, and symptomatic adjacent level disease (ASD).[2-9] In order to avoid those fusion-related side-effects, lumbar total disc replacement (TDR) has been introduced. However, TDR has also been associated with drawbacks, such as subsidence, dislocation, or malposition of the implant.[10-12]

Subsidence of a TDR, defined as the penetration of the prosthetic endplate into the vertebral endplate (Figure 4.1), is a frequently documented complication.[10,11,13-16] Subsidence occurs presumably due to non-central implantation(17, 18), implant undersizing[19,20], or reduced bone quality[21]. It may ultimately lead to spontaneous fusion of the vertebral segment or to failure of the TDR.[14,22] Consequently, patients with symptoms and radiographic subsidence, even without clear signs of wear or displacement, may undergo revision surgery.[22] However, there are no studies describing the relation between the occurrence of subsidence and signs or symptoms of the patient. The purpose of this study was to investigate to what extent subsidence of the TDR is related to clinical outcome. A secondary goal was to investigate if subsidence could be predicted by the position and relative size of the TDR on the direct-postoperative radiographs.

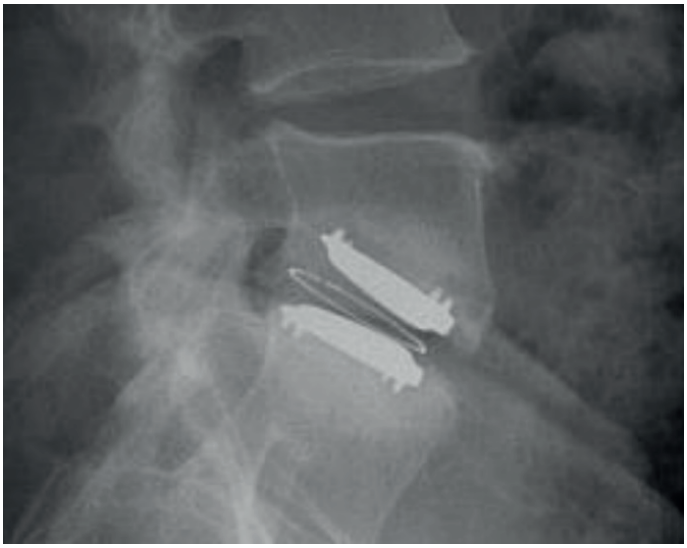

Figure 4.1 Example of SB Charité III TDR.

Materials and methods

Patient selection

The current study was approved by the local medical ethics committee METC Z (16-N-22) and registered at the Dutch Trial Registry (NTR5710). The medical records of all patients who underwent a TDR using an SB Charité III (Waldemar Link, Germany; DePuy Spine, Raynham, MA) between 1994 and 2000 (in 1998 a bioactive hydroxyapatite coating of the prosthetic endplates was introduced) at the Zuyderland Medical Centre, Sittard, The Netherlands were reviewed.

TDR had been performed by a single surgeon for the treatment of patients with lumbar DDD, causing predominant axial low back pain. Care was taken intra-operatively, to avoid violation of the bony endplate by the implant. The diagnosis was based on plain standing radiographs of the lumbar spine taken in antero-posterior (AP) and lateral views. Preoperatively, all patients had undergone fluoroscopically guided provocation discography to confirm a painful disc. No facet joint injections had been performed. Nerve root compression and/or spinal stenosis was considered as a contraindication for TDR. All patients were contacted with the request to visit the outpatient clinic for clinical evaluation and AP and lateral radiographs.

Radiological analysis

Subsidence as assessed by penetrated bone volume

A custom developed and validated software package implemented in Matlab (Matlab R2017b, Mathworks, MA) was used to create a 3-dimensional graphical representation of the implant.[20] By projecting the prosthetic endplate on the plane representing the vertebral endplate, the Penetrated Bone Volume (PBV) was calculated in mm^3 (Figure 4.2). The dimensions (width/length) of the prosthetic endplate were based on the size of the circular polyethylene insert, as documented in the patient's operative records. The prosthetic endplate was represented by parabolic functions for the anterior/posterior sides. This resulted in a shape that well matches the actual endplate (Figure 4.3). The PBV was calculated simultaneously for both the upper and lower part of the TDR and these values were added together.

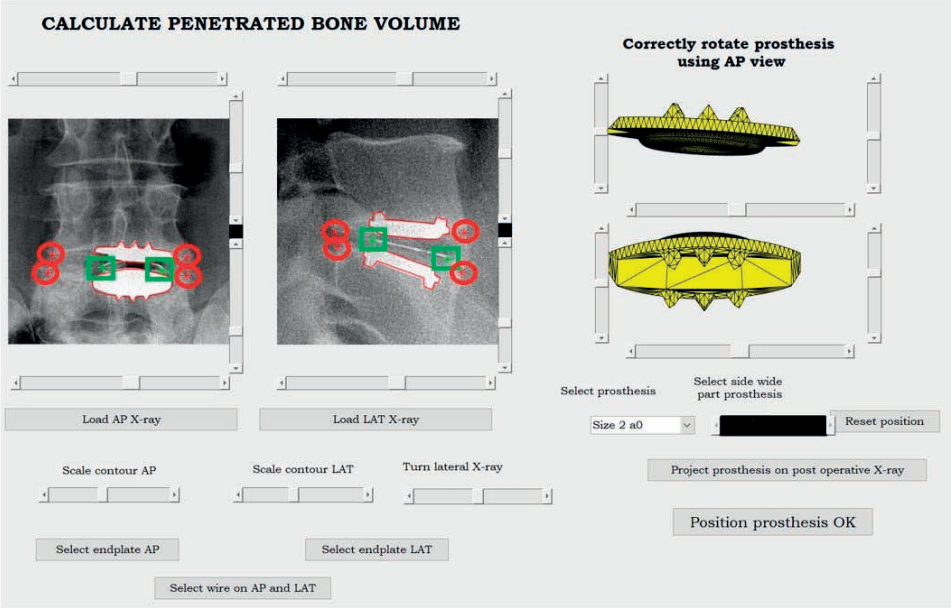

Figure 4.2 The 3-dimensional graphical representation of the TDR implant in relation to the bony endplates. This representation can be rotated manually until its contour best replicates the outline of the implant on both AP and lateral radiographs. Next, the most lateral left and right points of the bony endplate on the AP radiograph and the most anterior and posterior points of the bony endplate on the lateral radiograph were identified (red circles). Similar points had to be indicated on the metal ring of the circular polyethylene insert (green squares). The latter were used to correct for the difference in magnification factor between the AP and lateral radiograph of the same patient.

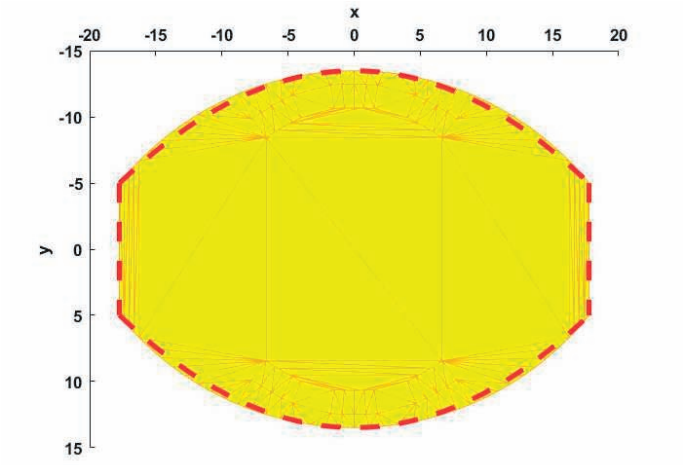

Figure 4.3 Bottom view of the graphical TDR representation, where the red lines indicate the contour of the used surface for calculating the PBV.

Subsidence as assessed by angular rotation (AR)

A second custom-developed software package implemented in Matlab was used to simultaneously display AP and lateral radiographs, direct post-operative and at last follow-up. On both the AP and lateral image the angle between the prosthetic and the vertebral endplate was calculated for the upper and lower part of the prosthesis (Figure 4.4.), using Cobb's method.[23,24] The highest value (upper- or lower part) was used for this analysis.[15] Analyses were done for the direct-post-operative- and for the last follow-up radiographs. The differences (Δ) between the AR at last follow-up and direct-post-operative (upper- and lower part) for each individual patient were calculated. The highest value was used for this analysis.

Areal Undersizing Index (AUI)

Using the same custom Matlab software package the potential mismatch between the surface area of the vertebral ($A_{vertebra}$) and the prosthetic endplate area A_{TDR} was determined (Figure 4.5). For this analysis, the vertebra and the prosthesis were assumed to be parabolic and the surface area was calculated as: $A=\pi * a * b$ for both the vertebrae ($A_{vertebrae}$) and TDR (A_{TDR}). Subsequently, the AUI was determined on the upper and the lower part of the prosthesis. The highest value (least coverage) was used for the analysis.

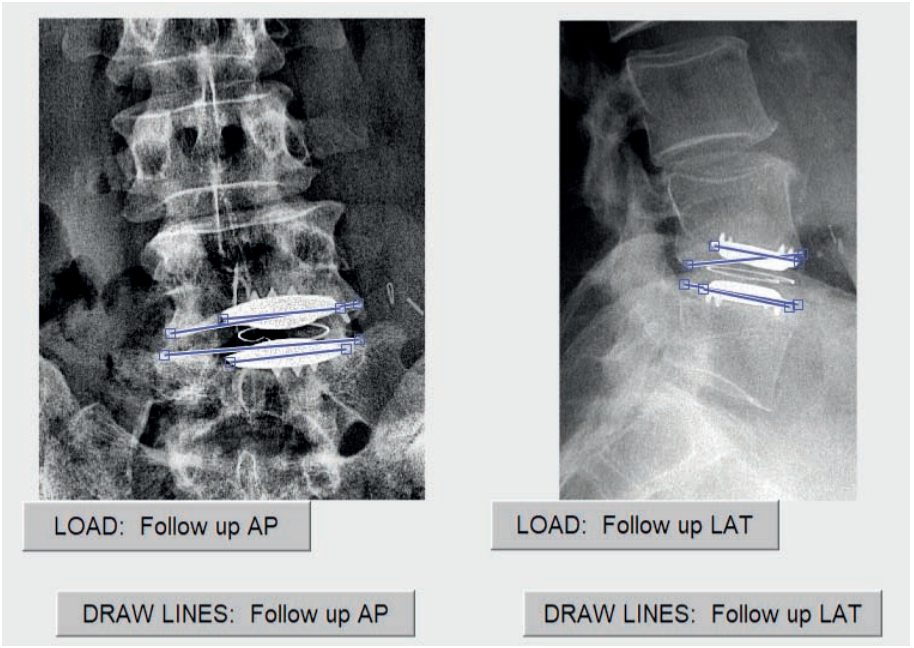

Figure 4.4 Angular rotation between the vertebral- and prosthetic endplate on an AP and LAT radiograph.

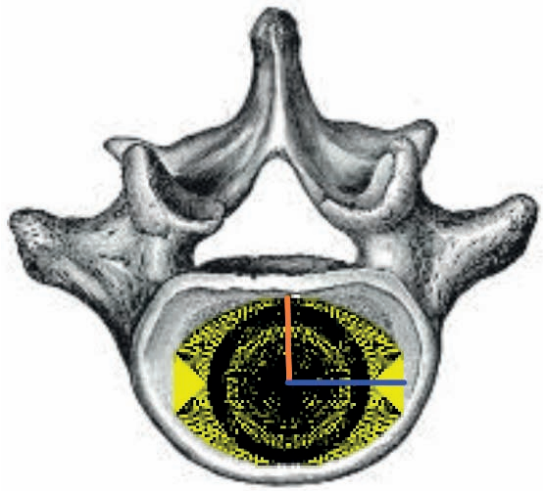

Figure 4.5 Representation of the semi-major axis (blue line) and semiminor axis (orange line) of the ellipse fitted around the prosthesis.

A value of zero implies that the contour of the TDR is perfectly matched with the contour of the vertebrae whereas a large value indicates undersizing of the implant.

Implantation asymmetry

Using the same Matlab package, Implantation Asymmetry (IA) was defined as the shortest distance (d) between the middle of both the vertebral- and the prosthetic endplate (Figure 4.6), divided by the corresponding vertebral endplate diameter. The measurements were done for the upper and lower part of the TDR, the highest value was used for the analysis. The differences (Δ) between the IA at last follow-up and direct-postoperative (upper- and lower part) for each individual patient were calculated. The highest value was used for this analysis.

$$\text{Areal Undersizing Index} = \frac{A_{\text{vertebra}} - A_{\text{TDR}}}{A_{\text{vertebra}}}$$

A value of zero implies that the prosthesis is perfectly aligned with the vertebrae, whereas a large value indicates a translation from the center. These values were measured on both the AP and lateral radiographs such that the symmetry can be quantified in two directions.

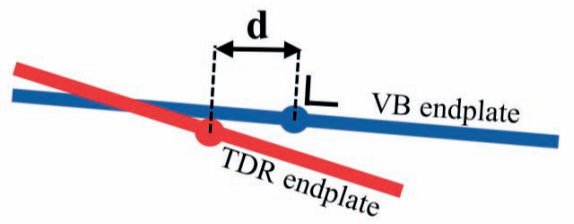

Figure 4.6 Implant asymmetry in percentage is the shortest distance (*d*) between the middle of both the vertebral and the prosthetic endplate, divided by the corresponding vertebral endplate diameter (blue line).

Clinical outcome evaluation

At last follow-up, back- and leg-pain intensity was recorded in all patients with a Visual Analog Scale (VAS, 0 to 100, 100 being 'worst pain'). The highest value was used for the analysis. Functional well-being was evaluated using Oswestry Disability Index (ODI, 0 to 100, 100 being maximally disabled)

Data analysis and statistics

All radiological measurements were performed by two independent observers, who were not involved in patient care (JK, VV). Mean values of their measurements were calculated. The interclass correlation coefficient (ICC) was used to quantify agreement between the two observers. Patients were assigned to a success- or failure-group based on their reported VAS- and ODI-score (failure was defined as VAS ≥50 in combination with an ODI ≥40).[16,25] In addition, patients with a revision by spinal fusion were included if both the radiographs direct post-operative and before their revision were available. They were all considered as failures of the TDR. The independent samples t-test was used to test for differences in the means of the radiological parameters between both groups. Using receiver operating characteristic (ROC) curves, possible threshold values were analyzed. A cut-off p-value of <0.05 was considered statistically significant. All analyses were performed using IBM SPSS (Version 23.0).

Results

Study population

Altogether 225 patients who had undergone a TDR at level L4-L5 and/or L5-S1 were identified, 16 patients had deceased (7.1%). The remaining 209 patients were contacted by mail and subsequently by phone, with the request to visit our outpatient clinic for. A

total of 152 patients (72.7%) were available for analysis. In 32 patients (15.3%) a revision by spinal fusion had been performed prior to our study. In only 5 patients this revision was because of subsidence or malposition of the implant. In the remaining patients the reason for revision was facet joint degeneration (n=14), ASD (n=10), or dislocation of the implant (n=3). In 8 out of these 32 patients, a complete set of radiographs was available and they were included for analysis. Informed consent was acquired in all patients.

Mean follow up after implantation was 16.7 years (median 16.4, range 13.6-23.0 years). In 18 patients (15.0%) the direct post-operative radiographs were not available. The remaining 102 patients were included for radiological analysis. Patient characteristics are listed in Table 4.1. Due to over-projection of the pelvis on the AP radiographs, for patients with a single TDR at L5-S1, the PBV, AUI and IA-AP could not be determined (n=56). Consequently, in 110 patients the AR and IA-LAT and in 54 patients the PBV, AUI and IA-AP could be determined. In only 4 patients a dual-energy X-ray absorptiometry (DEXA)-scan was available, hence we were unable to report on bone mineral density in relation to the occurrence of subsidence.

Table 4.1 Summary of subgroup patient demographic and surgical data presented as mean (standard deviation) or proportions (%).

	Patients (n=128)
Males, number	58 (45.3)
Mean age at time of surgery in years	42.6 (7.3)
Previous spinal surgery	24 (18.8)
Surgical levels	
L2-L3	1 (0.8)
L3-L4	2 (1.7)
L4-L5	64 (50.0)
L5-S1	78 (60.9)
Number of levels (one: two)	111:17
Indication for lumbar disc replacement (n=125)	
DDD without any other accompanying pathologies	91 (72.8)
DDD with a disc herniation and predominant axial low back pain	19 (15.2)
DDD following a discectomy	15 (12.0)

DDD=Degenerative Disc Disease.

Radiological analysis in relation to clinical outcome

High ICC between the two observers were found for AR ($R \geq 0.90$, $p<0.01$), IA ($R \geq 0.88$, $p<0.01$), AUI ($R \geq 0.85$, $p<0.01$), and especially PBV ($R \geq 0.972$, $p<0.01$). As shown in Table 4.2, there was a significant difference for AR (5.58° vs. 6.80, p=0.047), but no significant differences in the mean values for AR, IA, PBV, and AUI direct-postoperative (DPO) between the success- (N=61) and failure group (N=49). At last follow-up (LFU) both the AR (8.89° vs. 6.51°, p=0.019) and PBV (1757.2 mm^3 vs. 1058.7 mm^3, p=0.003) were significantly higher in the failure- compared to the success-group. When the differences

for the mean values between LFU and DPO were calculated, again for AR (ΔAR, 4.33° vs. 1.83° for the failure- and success group respectively, p=0.001) and PBV (ΔPBV, 1448.4 mm^3 vs. 747.3 mm^3 for the failure- and success group respectively, p=0.003) a significant difference was observed. Both PBV-LFU and ΔPBV were significantly higher in patients with a revision, compared to those in the success-group (p=0.009 and p=0.001 respectively). No significance differences, between the patients with (n=68) or without (42) the porous coating of the endplates, were observed.

Table 4.2 Mean values (standard deviation) of the success- and failure group and the differences (95% confidence interval) between the two groups.

	N	Success group (N=61)	Failure group (N=49)	Differences (Δ)	P-value[1]
AR post-operative	110	5.57° (3.34)	6.80° (2.94)	1.22 (-0.19 – 2.42)	0.047
AR at follow up		6.51° (4.14)	8.89° (5.92)	2.37 (0.49 – 4.35)	0.019
AR increase (ΔAR)		1.83° (1.83)	4.33° (4.39)	2.50 (1.14 – 3.87)	0.001
IA LAT post-operative	110	6.67% (4.85)	6.75% (7.88)	0.08 (-2.40 – 2.61)	0.934
IA LAT at follow up		7.01% (4.66)	6.37% (4.58)	-0.64 (-2.49 – 1.22)	0.496
IA LAT increase		3.03% (2.42)	4.11% (6.79)	1.08 (-0.80 – 2.96)	0.256
PBV post-operative	54	311.4 mm^3 (542.8)	308.8 mm^3 (555.3)	-2.62 (-295.0 – 289.9)	0.986
PBV at follow up		1058.7 mm^3 (890.3)	1757.2 mm^3 (951.0)	698.5 (195.6 – 1201.3)	0.007
PBV increase (ΔPBV)		747.3 mm^3 (736.7)	1448.4 mm^3 (913.9)	701.0 (249.0 – 1153.1)	0.003
IA AP post-operative	54	4.84% (2.98)	6.39% (4.59)	1.55 (-0.62 – 3.71)	0.157
IA AP at follow up		4.87% (3.10)	8.09% (9.50)	3.22 (-0.72 – 7.16)	0.107
IA AP increase		1.93% (1.22)	3.40% (7.05)	1,47 (-1.35 – 4.29)	0.299
AUI post-operative	54	0.50(0.06)	0.53(0.06)	0.03 (-0.01 – 0.06)	0.132

AR=Angular Rotation; IA=Implant Asymmetry; PBV=Penetrated Bone Volume; AUI= Area Undersizing index [1] Independent t-test.

Subsequently, ROC-curves were plotted for the occurrence of failure in relation to AR, IA, AUI, or PBV. Possible threshold values were determined by minimizing the false positive and false negative classifications (Table 4.3). A threshold of 6.23° was obtained for AR-LFU (Area Under the Curve (AUC) 0.625, p=0.026). For ΔAR an increase over time of 1.85° (AUC 0.685, p=0.001) was associated with failure. For PBV-LFU a threshold of 1223 mm^3 (AUC 0.724, p=0.005) was determined and for ΔPBV an increase of 829 mm^3 (AUC 0.723, p=0.003) was established. For IA and AUI no significant associations were seen. When applying these thresholds for PBV, 27 (54.0%, PBV-LFU) and 23 (46.0%, ΔPBV) of the studied patients without a revision (N=51) have radiographic subsidence.

Table 4.3 ROC curve association for failure presented as the area under the curve (standard error).

	N	Area under the Curve	Optimal cut-off value	p-value
AR post-operative	110	0.629 (0.053)	4.35°	0.021
AR at follow up		0.625 (0.054)	6.23°	0.026
AR increase (ΔAR)		0.685 (0.054)	1.85°	0.001
IA LAT post-operative	110	0.514 (0.058)	NA	0.811
PBV post-operative	54	0.509 (0.081)	NA	0.910
PBV at follow-up		0.724 (0.069)	1223 mm^3	0.005
PBV increase (ΔPBV)		0.732 (0.068)	829 mm^3	0.003
IA AP post-operative	54	0.592 (0.084)	NA	0.262
AUI post-operative	54	0.638 (0.078)	NA	0.092

AR=Angular Rotation; IA=Implant Asymmetry; PBV=Penetrated Bone Volume; AUI=Area Undersizing index.

Subsidence in relation to the position and relative size of the TDR

To investigate whether subsidence could be predicted by the position and relative size of the TDR on the direct-postoperative radiographs, we also investigated associations between position as measured from these radiographs and symptomatic subsidence as outcome. We defined symptomatic subsidence as a PBV-LFU of ≥1223 mm^3 or a ΔPBV of ≥829 mm^3, since both threshold values displayed the largest AUC. In addition, both can detect parallel subsidence, in contrary to ΔAR. In 7 patients (6.4%) a ΔPBV of ≥829 mm^3 with a ΔAR <1.85°, indicative for parallel subsidence, was observed. ROC-curves were plotted for both PBV-LFU (Table 4.4) and ΔPBV (Table 4.5) in relation to AR, IA, and AUI measured direct-post-operatively.

Table 4.4 ROC curve predictors for subsidence defined as a Penetrated Bone Volume at follow-up ≥1223 mm^3 presented as the area under the curve (standard error).

	N	Area under the Curve	Optimal cut-off value	p-value
AR post-operative	110	0.690 (0.075)	3.96°	0.022
IA LAT post-operative	110	0.612 (0.080)	NA	0.176
IA AP post-operative	54	0.501 (0.084)	NA	0.992
AUI postoperatieve	54	0.750 (0.074)	0.50	0.002

AR=Angular Rotation; IA=Implant Asymmetry; AUI=Area Undersizing index.

The occurrence of symptomatic subsidence defined as a PBV-LFU of ≥1223 mm^3 is associated with an AR-DPO of ≥ 3.96° AUC 0.690, P=0.022) and with an AUI-DPO of >0.50 (AUC 0.750, p=0.002). When the occurrence of symptomatic subsidence was defined as a ΔPBV of ≥829 mm^3, only an association with an AUI-DPO of <0.51 (AUC 0.718, p=0.008) was determined. For IA no significant associations were seen.

Table 4.5 ROC curve predictors for subsidence defined as a Δ Penetrated Bone Volume at follow ≥829 mm^3 presented as the area under the curve (standard error).

	N	Area under the Curve	Optimal cut-off value	p-value
AR post-operative	110	0.597 (0.081)	NA	0.239
IA LAT post-operative	110	0.596 (0.082)	NA	0.247
IA AP post-operative	54	0.539 (0.084)	NA	0.633
AUI postoperatieve	54	0.718 (0.073)	0.51	0.008

AR=Angular Rotation; IA=Implant Asymmetry; AUI=Area Undersizing index.

Discussion

This study represents a long-term follow-up of patients after lumbar TDR for the treatment of symptomatic DDD, and is the first study to establish a clear relation between the occurrence of radiographic subsidence and signs or symptoms of patients. Furthermore, the occurrence of subsidence could be predicted by the AR and AUI of the TDR measured on the direct-postoperative radiographs. High ICC between the two observers were found, indicating high agreement between observers.
Subsidence may ultimately lead to spontaneous fusion of the vertebral segment or to failure of the TDR due to wear or displacement.[14] To quantify radiographic subsidence, different methods have previously been described. Lee et al. defined subsidence as an increase over time of 5° in AR, measured on lateral radiographs.[15] They found no significant difference in clinical outcome between the patients with or without subsidence. However, parallel subsidence cannot be detected using this method. In the present study we identified 7 patients (6.4%) with parallel subsidence.

Punt et al.[20] considered radiographic subsidence to be present if the PBV-LFU was more than 1300 mm^3 or if the PBV-LFU was between 700-1300 mm^3 in combination with an AR of more than 7.5°. These values are similar with our findings. However, in contrast to the current study, no direct-postoperative images were available. Consequently, they could not investigate whether initial malpositioning or migration over time of the implant had led to the apparent radiographic subsidence at last follow-up. In addition, no clinical outcomes were reported, so they could not look for an association between the occurrence of subsidence and signs or symptoms.

Radiographic subsidence in relation to clinical outcome

In the current study, we determined that at last follow-up both the AR and PBV were significantly higher in the failure-group (VAS ≥50 and ODI ≥40). This also applies when the differences between the mean values at last follow-up and direct-postoperative were calculated (ΔAR and ΔPBV). It must be noted that 40.2% of the patients (n=41) were classified as failures based on their clinical outcome, a number exceeding the

number of patients with a revision in our population (n=32). However, these findings indicate that there is a relation between the occurrence of radiographic subsidence in terms of PBV and AR and signs or symptoms of the patient. Having established this, performing revision surgery for patients with radiographic subsidence and signs or symptoms seems a more viable option. This finding does not imply that worse clinical outcome is exclusively due to radiographic subsidence in all patients. Using ROC-curves, clinically applicable threshold values (ΔPBV≥829 mm^3 or PBV-LFU≥1223 mm^3) were obtained to assess which patients are at risk for symptomatic subsidence and were most likely to benefit from revision surgery.

Symptomatic subsidence in relation to the position and relative size of the TDR

ROC-curves were plotted, to investigate whether symptomatic subsidence could be predicted by the position and relative size of the TDR on the direct-postoperative radiographs. It seems that the AR should not exceed 4°. In addition, a reduced risk of symptomatic subsidence was found if at least 50% of the area of the bony endplate of the vertebra was covered by the TDR endplate. This value is consistent although slightly lower than the 60% described by Punt et al.[20] We believe that our threshold is a better representation because in the current study, not only patients with clinical problems after receiving TDR were included, but also asymptomatic patients, and a correlation with clinical outcome was established.

Initially, the relation between implant size and failure of the TDR was emphasized not enough. Gstoettner et al. reported a maximum allowed distance of 5 mm, between the edges of the TDR- and vertebral endplates on either side on both AP an lateral views, to prevent subsidence.[19] In the current study, mainly (98%) size 2 (25-31.5 mm) to 4 (29-38.5 mm) of the Charité III lumbar TDR were inserted. We can calculate the AUI when applying their method for the different sizes using the product specifications. Doing so, for size 2 an AUI of 0.46 and for size 4 an AUI of 0.41 was calculated (minimal coverage between 54-59%). These values are comparable with our findings. Similar to our results, in this study it was strongly advised to use whenever possible, the larger size Charité III TDRs.

The present study did not find an association between implantation asymmetry and clinical outcome or the occurrence of subsidence. A study of McAfee et al.[18] found that non-central implantation of the Charité TDR (n=205, follow-up 24 months), negatively affected clinical outcome and range of motion. No associations with the occurrence of subsidence were studied. Possibly, the effect of non-central implantation does not influence clinical outcome by subsidence or diminishes over time.

Study limitations and strengths

The current study's main limitation is its retrospective nature. We were only able to report on the changes in AR and PBV between directly post-operative and at last follow-up, which was not a standardized interval. In addition, we were only able to report on 8 out of the 32 patients with a revision of their TDR. Therefore it was not possible to correlate the obtained threshold values for symptomatic subsidence, with the likelihood of a revision. The mean follow-up of 16.7 years is substantial and might explain the relatively large number of patients who were lost to follow-up, mainly caused by patients who had died or could not be retrieved. In only 15% of the patients the direct post-operative radiographs were not available. Therefore, the number of patients included in this study is such that the outcomes may be considered valid and representative. Although the Charité III total disc replacement (TDR) is since 2012 no longer available on the market, the basic design features of many TDRs used today, are still very comparable and we think important lessons can be drawn for other designs as well. Subsidence is a recognized concern in TDR surgery and this is the first study to report on the association between radiographic subsidence and clinical outcome. In addition, this study indicates that occurrence of symptomatic subsidence is related to the position and relative size of the TDR, which are factors that can be optimized by the surgeon pre- or intraoperatively.

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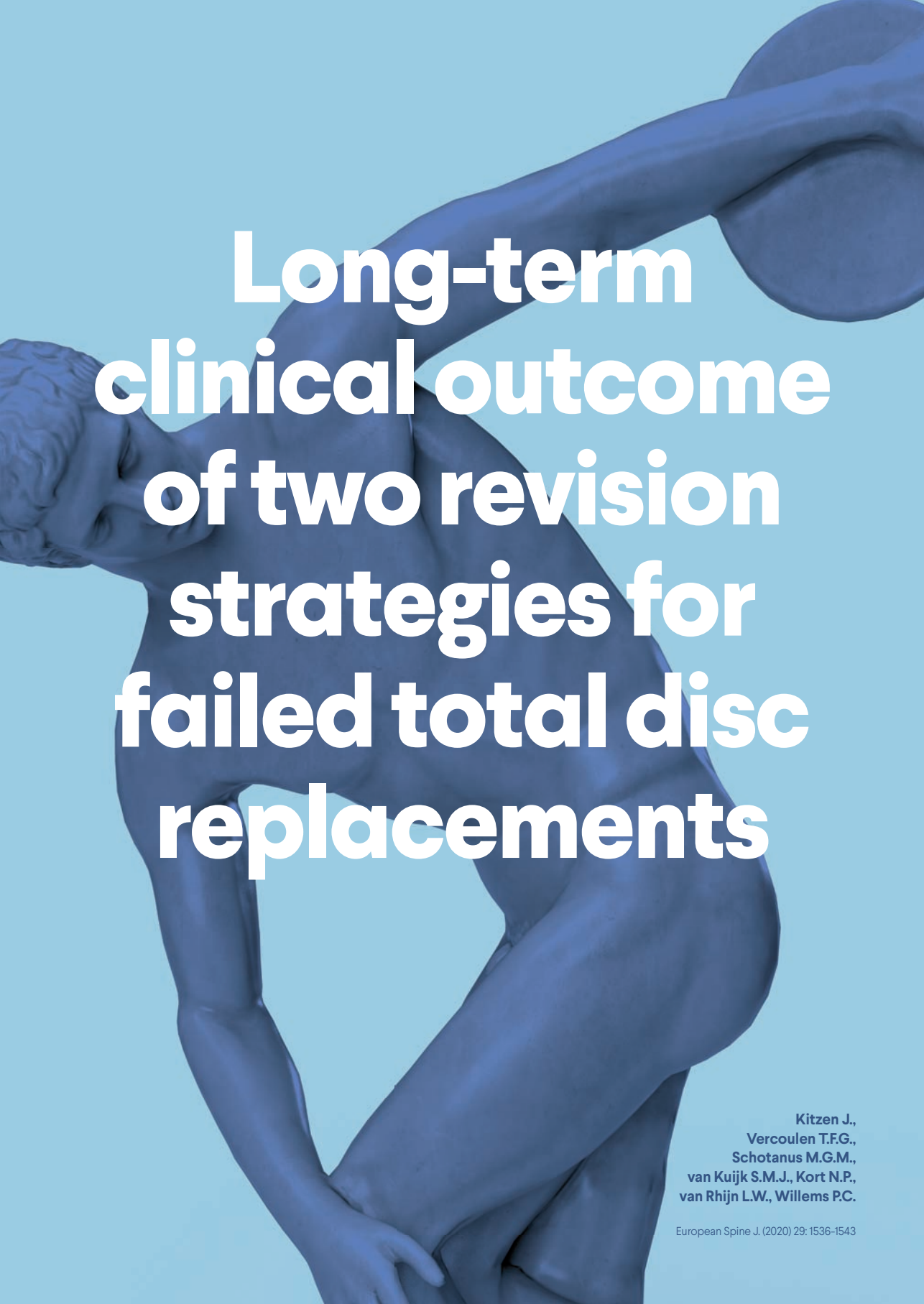

Long-term clinical outcome of two revision strategies for failed total disc replacements

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Abstract

Purpose

To compare the long-term clinical results and complications of two revision strategies for patients with failed total disc replacements (TDR).

Methods

In 19 patients, the TDR was removed and the intervertebral defect was filled with a femoral head bone strut graft. In addition, instrumented posterolateral fusion was performed (removal-group). In 36 patients, only a posterolateral instrumented fusion was performed (fusion-group). Visual analogue scale (VAS) for pain and Oswestry Disability Index (ODI) were completed pre- and post-revision surgery. Intra- and post-operative complications of both revision strategies were assessed.

Results

The median follow-up was 12.3 years (range 5.3-24.3). In both the removal- and fusion-group, a similar (p=0.515 and p=0419, respectively) but significant decrease in VAS- (p=0.001 and p=0.001, respectively) and ODI-score (p=0.033 and p=0.013, respectively) at post-revision surgery compared to pre-revision surgery was seen. A clinically relevant improvement in VAS- and ODI-score was found in 62.5% and 43.8% in the removal group, and in 43.5% and 39.1% in the fusion group (p=0.242 and p=0.773 respectively). Removal of the TDR was associated with substantial intra-operative complications such as major vessel bleeding and ureter lesion. The percentage of late re-operations for complications such as pseudarthrosis were comparable for both revision strategies.

Conclusions

Revision of a failed TDR is clinically beneficial in about half of the patients. No clear benefits for additional TDR removal as compared to posterolateral instrumented fusion alone could be identified. Especially, when considering the substantial risks and complications, great caution is warranted with removal of the TDR.

Introduction

Fusion of a symptomatic lumbar spinal motion segment is still considered the gold standard of operative treatments of patients with degenerative disc disease (DDD) not responding to conservative care.[1-7] As spinal fusion is associated with side effects such as cranial facet-joint violations, loss of segmental motion, pseudarthrosis, and symptomatic adjacent level disease,[8,9] total lumbar disc replacement (TDR) has been introduced to avoid those fusion-related side-effects. However, TDR may have serious drawbacks[10-12], such as subsidence, facet joint degeneration, or dislocation or malposition of the implant, requiring surgical revision.[13-16] According to literature 6-14% of patients needed revision fusion surgery after TDR.[10,11,17-19]

There is an ongoing discussion whether revision surgery for failed TDR is beneficial, and if so, what the optimal revision strategy should be.[13,15,20,21] In a previous study within a smaller patient group at mid-term follow-up (mean 3.7 years, range 0.7-11.0), patients significantly improved in terms of pain and function after TDR removal combined with posterolateral instrumented fusion, whereas, improvement did not appear to be significant after posterolateral fusion alone. However, the VAS- and ODI-scores were comparable for both groups at both time points.[15] Therefore the potential benefit of TDR removal in addition to posterolateral fusion was not fully substantiated in this study, especially considering the significant additional risks and complications of this procedure.[13-16,22,23]

Up till now, little is known about the long-term effects of posterolateral instrumented fusion combined with TDR removal or fusion alone. The purpose of this study was to compare the long-term clinical results (minimal follow-up of 5 years) and complications of these two revision strategies for patients with a failed SB Charité III TDR.

Materials and methods

Patient selection

The current study was approved by the Medical Ethics Committee (MEC) Z (16-N-22) and registered at the Dutch Trial Registry (NTR5710). The medical records of all patients who had undergone a TDR by a single surgeon using a SB Charité III between 1989 and 2003 were reviewed. After evaluation, in 63 patients one or more revision spinal fusion operations had been performed at the Zuyderland Medical Center in Sittard-Geleen or at the Maastricht University Medical Center in Maastricht, between 1991 and 2014. Informed consent was acquired in all patients. Indications for revision were recurrent back and/or leg pain with failure of appropriate conservative measures and the presence

of a TDR-related pathology such as facet joint degeneration, adjacent segment disease (ASD), malposition, or subsidence as determined by plain radiographs, CT-scan, MRI, and/or facet blocks (Table 5.1).

Clinical outcome measurements

The clinical evaluation included a Visual Analog Scale (VAS) for pain (0-100 points) and the Oswestry Disability Index (ODI) for function (0–100 points). Minimally clinically important difference (MCID) was defined as at least 25% improvement,[2,15,21] or a minimal reduction of 20 points[24] in VAS-score between pre- and post- revision surgery.[2,15,21] For the ODI-score a minimal reduction of 12.8 point was applied.[24]

Statistical analysis

Patient characteristics at the time of revision were summarized using mean and standard deviation (SD), or count and percentage for categorical variables. Continuous outcome parameters were described using mean and standard error of the mean (SEM). The independent- and paired sample t-test were used to test for a difference in mean. Differences in the distribution of categorical variables were tested using the chi-square test. A multivariable logistic regression model was utilized to identify independent risk factors associated with an insufficient MCID (applied for both definitions) in VAS- or ODI-score at latest follow compared to pre-revision surgery. P values <0.05 were considered statistically significant.

Results

In total, 63 patients were included. In 25 patients, the TDR was removed and after removal of periprosthetic fibrous tissue and sclerotic bone, the intervertebral defect was filled with a femoral head bone strut graft. In addition, an instrumented posterolateral fusion was performed (removal-group). In the other 38 patients, posterolateral instrumented fusion alone, without TDR removal was performed (fusion-group). The type of revision procedure was chosen according to the patient's preference after a detailed explanation of the potential benefits and risks. The exception in this matter was malposition or migration of the TDR. In all these patients (n=6) the TDR was removed. The presence of heterotopic ossification (HO) did not influence this decision.[25] Patients with complaints attributed to ASD were only included when spinal fusion of both the index- and the affected adjacent segment was performed (n=8). The surgical technique of both surgeries (Figure 5.1) has been described in detail by de Maat et al.[14]

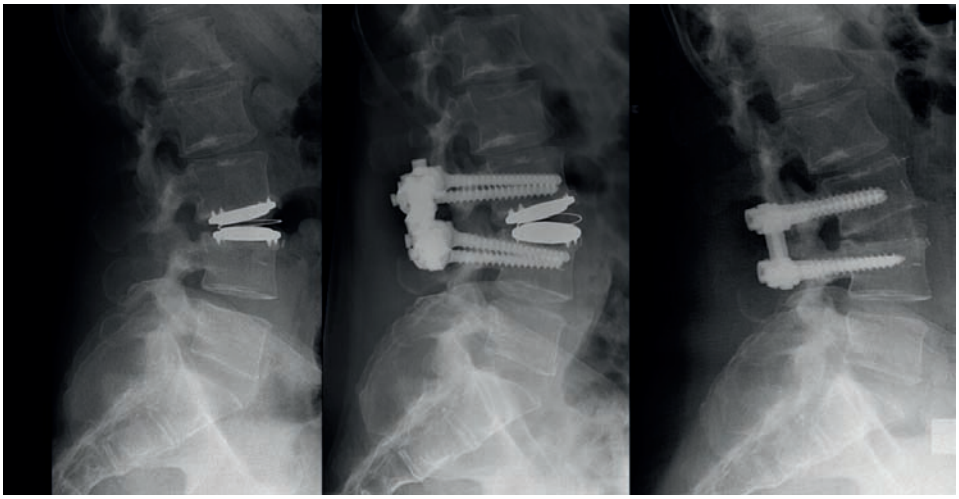

Figure 5.1 Example case before and after revision of the TDR by posterolateral instrumented spinal fusion and after second stage removal of the TDR.

For all 63 patients intra- and post-operative complications were assessed. At a minimum of five years follow-up, 8 patients (12.7%) were lost to follow-up. The median follow-up after revision surgery (n=55) was 12.3 years (range 5.3-24.3 years). This was 10.0 years (range 5.3-21.3 years) in the removal-group (n=19) and 14.3 years (n=36, range 5.7-24.3 years) in the fusion-group (p=0.008). In 16 patients (25.4%) pre-revision clinical evaluation was not available (3 patients in the removal- and 13 in the fusion-group). An overview of the included patients is shown in Figure 5.2. Because of persisting pain, in 8 patients within the fusion-group (22.2%), TDR removal was performed as a second stage revision surgery. In 6 out of these 8 patients, data was available before and after fusion (stage 1) and after removal of the TDR (stage 2).

There were no significant differences for the baseline characteristics with respect to gender, age at insertion of the TDR, body mass index (BMI), surgical levels, or number of operated levels between the two groups (Table 5.1). Significantly more patients had facet joint degeneration in the fusion-group (p=0.004), whereas more patients with either ASD or subsidence were in the removal-group (p=0.072 and p=0.093).

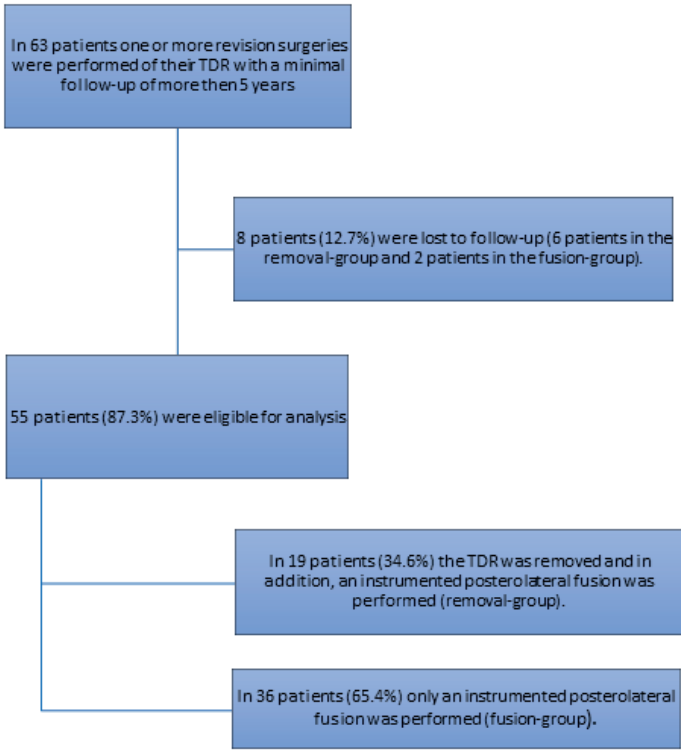

Figure 5.2 Overview of the included patients.

Table 5.1 Summary of patient- and clinical variables for TDR removal- and fusion-group.

	Removal-group (n=19)	Fusion-group (n=36)	P - value[1]
Males number (%)	6 (31.6)	13 (36.1)	0.737[1]
Mean age at time of TDR, years (SD)	42.4 (4.7)	40.4 (8.1)	0.341[2]
Age < 45 years at the time of TDR, number (%)	6 (31.6)	8 (22.2)	0.449[1]
BMI, mean (SD)	24.2 (2.8)	24.8 (3.5)	0.625[2]
BMI > 30, number (%)	0 (0.0)	2 (7.4)	0.401[1]
Previous surgery before TDR, number (%)	4 (21.1)	9 (25.7)	0.702[1]
Surgery between TDR and revision, number (%)	5 (26.3)	17 (47.2)	0.132[1]
Surgical levels			
L2-L3 (percentage)	1 (5.3)	1 (2.8)	0.640[1]
L3-L4 (percentage)	0 (0.0)	3 (8.3)	0.196[1]
L4-L5 (percentage)	11 (57.9)	19 (52.8)	0.717[1]
L5-S1 (percentage)	13 (68.4)	24 (66.7)	0.895[1]
Number of levels (one – two)	14 - 5	26 - 10	0.908[1]
Indication for revision surgery			
Facet joint degeneration (%)	5 (26.3)	24 (66.7)	0.004[1]
Adjacent disc disease (%)	5 (26.3)	3 (8.3)	0.072[1]
Subsidence or malposition (%)	9 (47.3)	9 (25)	0.093[1]

[1] Chi-square test; [2] Independent sample t-test.

VAS-scores

The mean ± SEM pre-revision VAS score was 79.7 ± 1.48 in the removal- and 77.5 ± 2.31 in the fusion-group (p=0.481). Post-revision VAS scores were 54.3 ± 5.93 and 57.4 ± 5.65 in the removal- and fusion-group, respectively (p=0.712). In both the removal- and the fusion group, a similar (p=0.515) but significant decrease in VAS-score (p=0.001 and p=0.001, respectively) at post-revision surgery compared to pre-revision surgery was seen (Figure 5.3A).

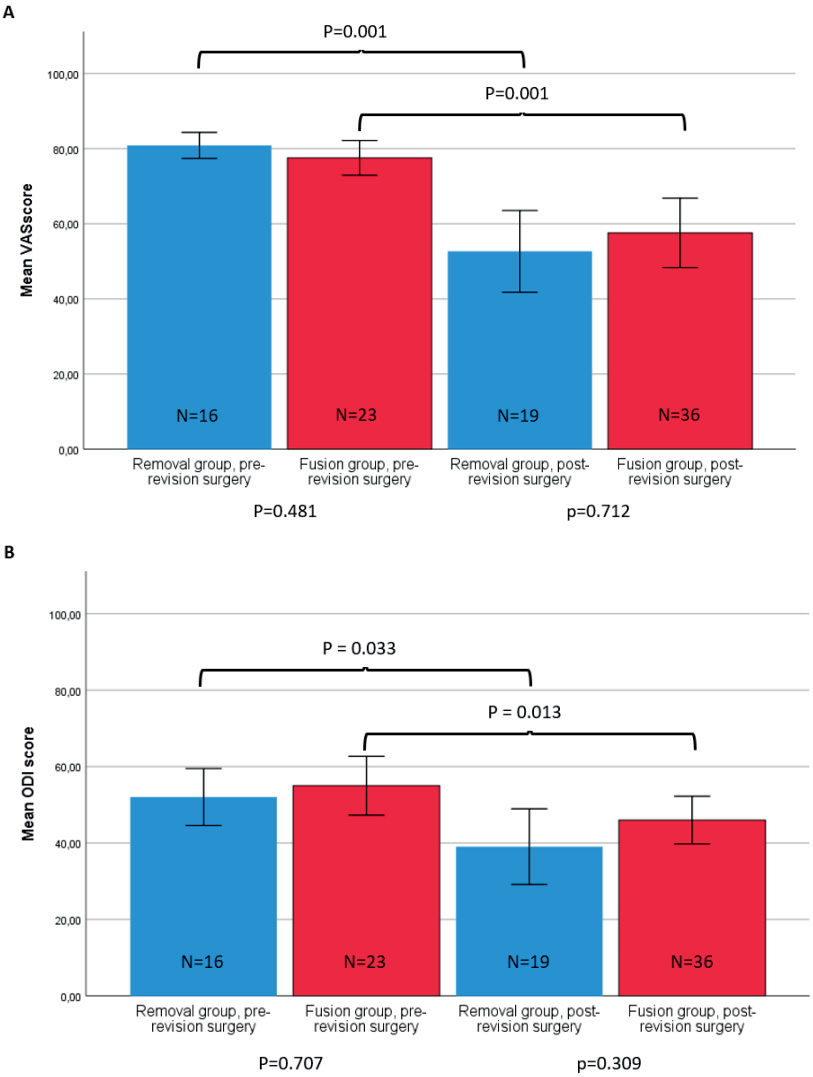

Figure 5.3 **A** Mean VAS scores for both groups pre- and post-revision surgery. **B** Mean Oswestry Disability Index for both groups during pre- and post-revision surgery. The error bars represent standard error of the mean

The percentage of improvement after revision surgery in both groups is shown in Figure 5.4A. When a minimal improvement of 25% is warranted, 10 out of 16 patients (62.5%) in the removal-group and 10 out of 23 patients (43.5%) in the fusion group showed a clinically relevant improved (p=0.242). If a minimal reduction of 20 points is applied, 9 out of 16 (56.3%) in the removal- and 11 out of 23 patients (47.8%) in the fusion-group improved (p=0.987).

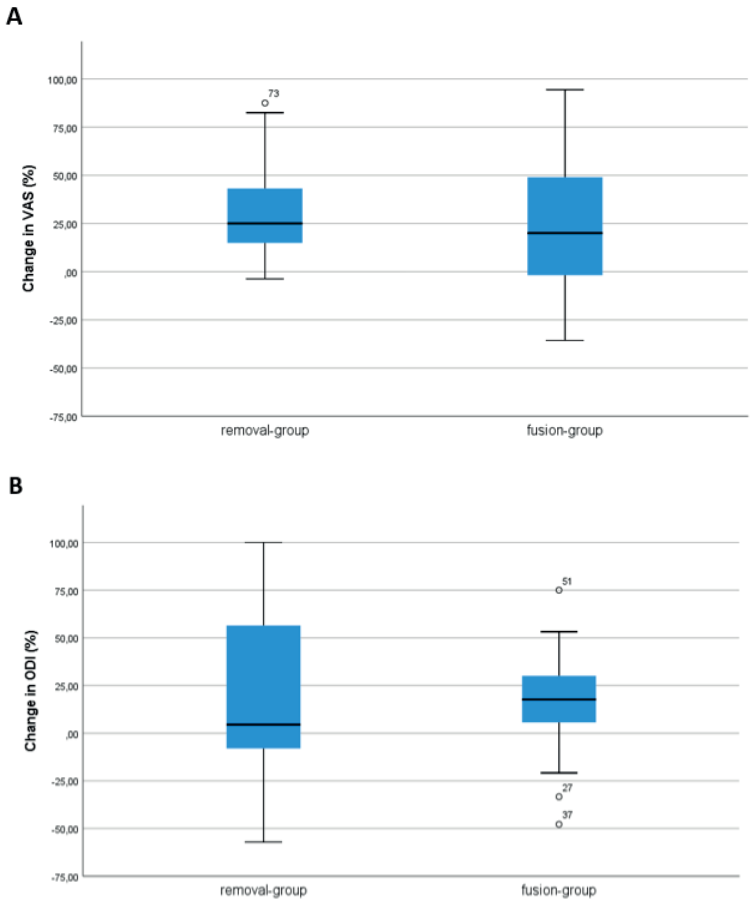

Figure 5.4 **A** Box plot with a percentage change in VAS-score in both revision strategy groups during pre- and post-revision surgery, **B** percentage change in ODI score in both revision strategy groups during pre- and post-revision surgery. The line represents a clinical success rate of 25%. The error bars represent the upper and lower quartiles

We considered the variables provided in Table 5.1 as potential risk factors for a lack of improvement in VAS-score. These variables were included in a multivariable logistic

regression model. Level L2-L3 and level L3-L4 had to be omitted because of too few events to reliably estimate the odds ratio (OR). None of the potential risk factors (including indications for revision surgery) were associated with a lack of clinically relevant improvement in VAS-score.

Oswestry disability index

The mean ± SEM pre-revision surgery ODI-score was 52.9 ± 3.87 in the removal and 55.0 ± 3.85 in the fusion-group (P=0.707). Post-revision ODI-scores were 40.0 ± 5.89 and 46.9 ± 3.79 in the removal- and fusion-group, respectively (p=0.309). In both the removal- and the fusion group, a similar (p=0.419) but significant decrease in ODI-score (p=0.033 and p=0.013, respectively) at post-revision surgery compared to pre-revision surgery was seen (Figure 5.3B).

The percentage of improvement after revision surgery in both groups is shown in Figure 5.4B. A clinically relevant improvement of 25% was present in 7 out of 16 patients (43.8%) in the removal- and in 9 out of 23 patients (39.1%) in the fusion- group (p=0.773). If a minimal reduction of 12.8 points is applied, 7 out of 16 patients (43.8%) in the removal- and 10 out of 23 patients in the fusion-group (43.5%) improved (p=0.411). When the abovementioned multivariable logistic regression model is applied, none of the potential risk factors were statistically significantly associated with a lack of clinically relevant improvement in ODI-score.

Second stage revision surgery

In the fusion group, eight patients with persisting symptoms underwent TDR removal as a second stage revision surgery after a median time of 3.3 years (range 1.2-4.4 years). After their second stage revision surgery a median follow-up of 7.4 years (range 1.4-11.4 years) was available. A difference in mean VAS-score of 14.6 ± 4.11 was seen post-revision surgery (stage 1), between the patients who underwent TDR removal at a later time-point and those who did not (p=0.880). There was not a clear difference for the mean ODI-score (2.5 ± 3.49, p=0.760).

Patients who underwent removal of the TDR as a second stage revision surgery had a slight but not substantial decrease in their VAS-scores (11.6 ± 7.20, p=0.396) and virtually no decrease in their mean ODI-scores (2.3 ± 5.1, p=0.512) at latest follow-up. Only in two out of 6 patients (33.3%) an MCID (both definitions) was achieved for both the VAS- and ODI-scores.

Complications

An overview of the complications for both revision procedures is shown in Table 5.2. One or more intra- or direct post-operative complications were reported in 7 patients (63.6%) in the removal-group and in 4 patients (36.4%) in the fusion-group (p=0.097), with a median time till complication of 0.16 months (range 0-12.1 months).

Table 5.2 Summary of the different complications for TDR removal- and fusion-group.

Different complications	Removal-group n=25 (%)	Fusion-group n= 38 (%)	Median time in months till complication (range)
Intra- or direct post-operative complications			0.16 (0.0-12.1)
Deep surgical site infection	2 (8.0%)	3 (7.9%)	
Small colon lesion	1 (4.0%)		
Rupture of small intestine	1 (4.0%)		
Major vessel bleeding	3 (12.0%)		
Lesion of the ureter	1 (4.0%)		
Malposition pedicle screw		1 (2.6%)	
Lung emboli	1 (4.0%)		
Reoperations for the treatment of persisting symptoms			70.1 (10.3-164.8)
Pseudarthrosis	5 (20.0%)	7 (18.4%)	
Adjacent segment disease		4 (10.5%)	
Junctional kyphosis	1 (4.0%)		

Intra-operatively, no complications were seen in the fusion group. In the removal group, one patient (4.0%) sustained a small colon lesion, and three patients (12.0%) had a major vessel bleeding (estimated blood loss >1500 cc). One of these patients sustained a lesion of the ureter as well, which necessitated resection of the left kidney at a second stage. In another patient with a major vessel bleeding, a lung embolus was diagnosed post-operatively. In one patient (4.0%) TDR removal was planned, however, due to an intra-operative rupture of the small intestine this procedure was abandoned and only posterior fusion was performed. This patient was thus included in the fusion group for further analysis.

Post-operatively in one patient (2.6%) in the fusion-group a malposition of a pedicle screw was diagnosed, which was revised at a second stage. In both groups (2, or 8.0% in the removal- and 3, or 7.9% in the fusion-group) deep surgical site infection of the dorsal wound, warranting debridement and lavage, was observed.

In six patients (24.0%) in the removal- and eleven patients (28.9%) in the fusion-group (p=0.558) a reoperation for persisting symptoms of low back pain was performed with a median time of 70.1 months (range 10.3-164.8) after revision. In both the removal- (n=5, 20.0%) and the fusion-group (n=7, 18.4%) pseudarthrosis occurred, necessitating revision posterior spinal fusion. In the removal-group one patient (4.0%) developed a junctional kyphosis, in the fusion-group four patients (10.5%) developed adjacent

segment disease. Both groups were treated with elongation of the levels previously fused.

Discussion

This study reports the long-term clinical results of two revision strategies for failed TDR with a minimal follow-up of five years (median of 12.3 years). Both revision strategies showed clinical improvement, with no additional benefits of removing the TDR in combination with anterior interbody fusion, as compared to posterolateral instrumented spinal fusion alone.

In a previous study within a smaller patient group at mean follow-up of 3.7 years (range 0.7-11 years) we reported a small benefit of TDR removal in terms of improvement of mean VAS- and ODI-scores.[15] However, in the current study mean VAS- and ODI scores were comparable for the removal- and fusion-group at both time points. Furthermore, the VAS- and ODI-score significantly improved in both groups compared to pre-revision surgery. Based on these results there was no clear benefit from removal of the TDR.

An MCID was found in 56.3-62.5% in the removal- and in 43.5-47.8% in the fusion-group for pain (VAS-score) and 43.8% and 39.1-43.5%, respectively for functionality (ODI-score). Although not statistically significant, MCID seemed slightly better in the removal group. These differences are however, less pronounced than previously reported.[15] Unfortunately, we did not obtain psychological testing, so we were not able to study the psychological profile in relation to clinical outcome. The results of additional TDR removal, as a second stage procedure, because of persisting complaints after posterolateral fusion were disappointing in most patients.

In the ongoing discussion about the optimal revision strategy for failed TDRs it is suggested that in case of an intact implant in an acceptable position, posterior fusion can be addressed for the treatment of recurrent back pain presumably caused by facet joint degeneration. When the TDR has subsided or mechanically failed, TDR removal could be considered.[15] However, in the current study, patients with subsidence of the TDR were treated in both groups and no significant changes in terms of VAS- and ODI-scores were seen at latest follow-up.

In a previous study by Punt et al. the periprosthetic fibrous tissues of 16 consecutive patients with TDR removal were investigated.[26] Results of that study demonstrated the presence of polyethylene wear particles and of peri-prosthetic inflammatory reactions around a failed TDR in 15 out of 16 patients. These findings were consistent with other studies.[27,28] It was therefore hypothesized that TDR removal might reduce back and leg

pain in failed TDRs because the source of wear debris generation is removed, which may diminish inflammatory mediated pain. However, in terms of both VAS- and ODI-scores, no additional benefits of removing the TDR was seen in this study.

An important point to consider is that removal of the TDR was associated with substantial intra-operative complications. This is consistent with other studies reporting considerable iatrogenic injury during revision exposure.[13-16,22,23] Moreover, the percentage of late re-operations (median 70.1 months) for complications such as pseudarthrosis, were comparable for both groups.

The current study was limited by its retrospective nature, and the fact that patients were not randomized but the type of revision procedure was chosen according to the surgeon's and the patient's preference. The number of patients included in any study has a vital influence on the outcome and whether a study is representative or not. We included a total of 55 patients with a minimal follow-up of five years. Only 8 patients (12.8%) were lost to follow-up. This study on revision surgery after TDR, reports on the largest number of patients and with the longest follow-up available in literature.

In conclusion, revision of a failed TDR is clinically beneficial in about half of the patients. No clear benefit from additional TDR removal as compared to posterolateral instrumented fusion alone could be identified. Especially when considering the substantial risks and complications, great caution is warranted with removal of the TDR.

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General Discussion

Valorization

General discussion

This thesis focused on the long-term clinical, radiographical, and functional outcome of the Charité III lumbar total disc replacement (TDR) and its revision strategies, in patients with chronic low back pain (LBP) caused by lumbar degenerative disc disease (DDD).

In **Chapter 2**, the long-term clinical outcome in terms of patient satisfaction, and complication- and revision rate after TDR was examined. Additionally, an assessment was made to identify patient- or surgical risk factors for worse clinical outcome and revision operations. It was found that the overall reoperation rate for patients with a lumbar TDR was 31.1% and that in 19.9% revision spinal fusion at the index level had been performed after a mean follow-up of almost 20-years.

In the debate on the use of TDR as a standard care of practice for patients with symptomatic lumbar DDD, deteriorating effect over the years and high rates of late revision operations are a recognized concern.[1,2] To assess this concern, long-term data are paramount.[3] There are few studies with a minimal follow-up of 10-years.[4-9] Those available report a reoperation rate between 5-33 per cent. A trend was seen that the earliest studies or those with longest follow-up reported less favorable outcomes.[5] This trend could be explained by the fact that in later years improvements have been made in terms of surgical technique, material properties such as adding hydroxyapatite coating on the prosthetic endplates, and more appropriate patient selection based on patient expectations and psychosocial profile.[2,4]

The vast majority of reoperations in **Chapter 2**, including revision spinal fusions, occurred in the first 10-years after TDR. This indicates that the fear of excessive late complications or reoperations following primary TDR cannot be substantiated. However, this study has a retrospective design and lacks a control group (either nonoperative or index spinal fusion), as can be attributed to most long-term follow-up studies.[4,6,7,9] These reoperation rates should then be compared with rates that have been published in literature on lumbar fusions. One large retrospective cohort study in adults who underwent lumbar fusion for degenerative spine disorders between 1990 and 1993 (n=2345) was identified. It showed a cumulative incidence of reoperations of 21.5% after 11-years follow-up.[10] This is similar to the revision fusion rate in the current chapter, but the overall reoperation rate in our cohort is higher at last follow-up. When we look at our reoperation rate after 11-years follow-up (27.7%), this difference is less pronounced, but still higher for TDR when compared to the fusion cohort. Data from the available randomized controlled trials (RCT) with a maximum follow-up of five years, report that TDR is not inferior to spinal fusion in terms of clinical outcome and revision rates.[11-18] The long-term follow-up of these trials will have to prove if these findings remain over time.

Rheumatoid arthritis, osteoporosis, age at the time of surgery <45 years, BMI >30 and previous spinal surgery were all associated with a worse clinical outcome after TDR in Chapter 2. Tropiano et al. showed similar results for age and previous spinal surgery.[19] In contrast to a study by Siepe et al.[2], multilevel TDR did not significantly increase the probability of revision surgery or poor clinical outcome. These findings are consistent with several other studies.[5,19,20] The level of placement of the TDR was not associated with an increase in revision surgery or a decrease in clinical outcome either. This again is consistent with the available literature.[21,22] The identification of patient- and surgical risk factors associated with worse clinical and functional outcome after TDR, may help in more appropriate patient selection for this procedure, which could help improve clinical outcome and decrease revision rates after future TDR.

In Chapter 3, the long-term incidence of adjacent segment disease (ASD) and residual-mobility after TDR was evaluated. TDR has been introduced in order to preserve motion at the affected level,[23,24] aiming to prevent the occurrence of ASD as seen after lumbar fusion.[25-28] The number of studies with a minimal follow-up of 10-years (mean 10-12 years) addressing the occurrence of residual-mobility after TDR is limited.[4,6,8,9] Those available, reported a mean range of motion (ROM) between 7.7˚-10.3˚ at last follow-up. However, none of these studies defined a minimal change in the sagittal alignment angles that had to be observed in order to conclude if a TDR had any sagittal motion or not (residual-mobility). Nor, did they make a comparison with clinical outcome. In the current study a mean ROM of 4.3° (range: 0˚-15.6˚) was measured. This is slightly lower than in the other studies, which may be explained by the longer follow-up duration (mean 16.7 years). Moreover, in studies where ROM was monitored over time, a gradual decline of the device mobility was noted, although without negatively impacting these patients' clinical outcomes.[9,29]

Residual-mobility was defined as a minimal change of 4.6° in the sagittal alignment angles at the index level of the TDR in Chapter 3. It appeared that in order to be sure with 95% certainty that a TDR has any sagittal motion left, at least 4.6° of motion should be observed on standard flexion-extension lumbar spine radiographs.[30] Doing so, residual-mobility was noted in only 38% of our patients at last follow-up. No significant associations were found between the different patient- or procedure-related characteristics, such as the level of placement or multilevel TDR, and the occurrence of residual-mobility. Moreover, no significant associations were observed between clinical outcome and residual-mobility. In contrast to our findings, only the retrospective study of Huang et al. (n=32, mean follow-up 8.7 years) reported an association between residual-mobility (ROM >5º) and worse clinical outcomes.[31]

Additionally, no significant relationship between residual-mobility and the occurrence of ASD was found. The current retrospective study lacks a control group, so unfortunately

no direct comparison between TDR and fusion regarding the occurrence of ASD could be made at long-term follow-up. However, this finding is similar to the results reported at short- to mid-term follow-up in a prospective study of Siepe et al.[32] (n=91) and an RCT by Zigler et al.[33] (n=261) Interestingly, in the study by Zigler et al. the risk of ASD following TDR is significantly lower when compared with spinal fusion at five years follow-up. However, the appearance of ASD does not significantly increase revision surgery for ASD or deteriorate clinical outcome.[33] It seems that TDR might have a protective effect against ASD, five years after the index surgery, but this effect is not directly related to residual-mobility or clinical outcome. It is interesting to investigate if this effect remains at longer follow-up and if it is clinically relevant.

As previously discussed in **Chapter 1,** biomechanical studies have shown that motion of a TDR differs from that of a normal disc in an intact spine.[34-36] Maybe not so much the extent of motion, but rather the quality of motion is the main factor in the occurrence of ASD. Other biomechanical studies have demonstrated altered loading patterns and increased facet joint pressure after TDR.[37-39] Siepe et al.[32] reported a significant increase of facet joint degeneration (FJD) at the index level after TDR and a significant decrease in ROM at the same level. This occurrence of FJD was associated with worse clinical outcome. In conclusion, development of FJD may be a stronger factor influencing clinical outcome after TDR than ASD. In **Chapter 2** and especially in **Chapter 5**, FJD was the main reason for a revision by spinal fusion.

In **Chapter 4**, it was investigated to what extent subsidence over time is related to clinical outcome. A secondary goal was to investigate if subsidence could be predicted by the position and relative size of the TDR on the direct postoperative radiographs. It is important to realize that patients with symptoms and radiographic subsidence, even without clear signs of wear or displacement, do undergo revision surgery.[40] However, as yet there are no studies describing the relation between radiographic subsidence and clinical outcome. This chapter established a clear relation between the occurrence of radiographic subsidence over time and worse clinical outcome. In addition, clinically applicable threshold values were obtained to assess which patients are at risk for symptomatic subsidence.

To quantify radiographic subsidence, different methods have previously been described. Lee et al.[41] defined subsidence as an increase over time of 5^{o} in angular rotation (AR), measured on a lateral radiograph. They found no significant difference in clinical outcome between the patients with or without subsidence. However, parallel subsidence cannot be detected using this method. Punt et al. considered radiological subsidence to be present if at last follow-up the penetrated bone volume (PBV) was >1300 mm^3 or if the PBV was between 700-1300 mm^3 in combination with an AR >7.5°. However, no direct post-operative images were available. Consequently, they could not

investigate whether initial malpositioning or migration over time of the implant had led to the apparent radiographic subsidence at last follow-up. Nor, did they report on possible associations between the occurrence of radiographic subsidence and clinical outcome.

In Chapter 4, patients were assigned to a success- or failure-group based on their reported VAS- and ODI-score (failure was defined as a revision by spinal fusion, or a VAS ≥50 in combination with an ODI ≥40) Both the AR and PBV were significantly higher at last follow-up in the failure-group. This also applies when the differences between the individual values at last follow-up and directly post-operative were calculated (ΔAR and ΔPBV). These findings indicate that there is a relation between the occurrence of radiographic subsidence and a worse clinical outcome of the patient. Having established this, performing revision surgery for patients with radiographic subsidence and signs or symptoms seems a more viable option. The next step was to identify patients with this so-called symptomatic subsidence, and ROC-curves were plotted to determine threshold values for the occurrence of failure. Thus, symptomatic subsidence was defined as a PBV at last follow-up of ≥1223 mm^3 or a ΔPBV of ≥829 mm^3. These thresholds can be of assistance to identify patients more likely to benefit from revision surgery for subsidence.

Finally, it was determined that an AR of more than 4° direct-postoperatively, or a coverage of the vertebral endplate by the TDR endplate less than 50%, are associated with the occurrence of symptomatic subsidence at last follow-up. The findings about the relative size of the TDR are consistent with the retrospective studies by Punt et al.[42] and Gstoettner et al.[43] It is important to emphasize that AR and undersizing of the TDR are factors that can be optimized by the surgeon pre- or intraoperatively.

Chapter 5 investigated the optimal revision strategy for a failed TDR. It indicates that revision by spinal fusion of a failed TDR is clinically beneficial in about half of the patients at minimal 5-years follow-up. No clear benefit from additional TDR removal as compared to posterolateral instrumented fusion alone could be identified. Especially, when considering the substantial risks and complications associated with TDR removal, this should not be advocated routinely.

As yet, little is known about the long-term effects of posterolateral instrumented fusion combined with TDR removal or fusion alone. Besides the study by Punt et al.[44] with a mean follow-up of 3.7 years (range 0.7-11 years), no other study made a comparison between different revision strategies based on clinical outcome. The few studies available on revision surgery for failed TDR focus on revisability, surgical techniques, and their complications.[44-49] In Chapter 5, the minimal follow-up was set to five years. Consequently, we were able to not only investigate the long-term clinical outcome, but

also report on late reoperations for the treatment of persisting symptoms such as ASD, junctional kyphosis, or pseudarthrosis.

No significant benefit in the minimally clinically important difference (MCID) was seen for additional TDR removal as compared to posterolateral instrumented fusion alone. The results of additional TDR removal, as a second stage procedure, because of persisting complaints after posterolateral fusion, were disappointing as well. TDR removal is associated with considerable intra-operative complications such as major vessel bleeding and intestinal injury. This finding is consistent with several other studies, reporting iatrogenic injury during revision exposure.[44-49] Whereas, the percentage of (late) re-operations, were comparable for both revision procedures. It has been suggested that when the TDR has subsided or mechanically failed, TDR removal should be considered.[44] However, patients with subsidence of the TDR were present in both revision groups and no significant differences in terms of VAS- and ODI-scores were seen for these patient at last follow-up. The exception in this matter is evident malposition or migration of the TDR, in all these patients the TDR was removed.

Finally, an argument in favor of removal of the TDR could be the occurrence of polyethylene wear.[50-52] Several studies demonstrated the presence of polyethylene wear particles and inflammatory reactions in periprosthetic fibrous tissues around a failed TDR.[50-52] It was therefore hypothesized that removal of the TDR may diminish inflammatory mediated pain, since the source of wear debris generation is removed.[50-52] However, we did not found a significant difference in MCID for the VAS-score when both revision procedures were compared. Therefore, restraint should be advocated on TDR removal.

Conclusions and recommendations

Based on the results of this thesis the following conclusions and recommendations can be made:

- Fear of excessive late complication- or revision rates following primary TDR cannot be substantiated, since the vast majority of all reoperations occurred in the first 10 years after TDR **(Chapter 2)**;
- Residual-mobility is not associated with the occurrence of ASD at long-term follow-up. Both residual-mobility and ASD seem unrelated to long-term clinical outcome **(Chapter 3)**;
- Subsidence of a TDR is associated with worse clinical outcome and its occurrence can be predicted by incorrect placement intraoperatively or size mismatch of the TDR (**Chapter 4**);

- Revision of a failed TDR is clinically beneficial in about half of the patients with no benefit from additional TDR removal as compared to standalone posterolateral instrumented fusion **(Chapter 5)**.

Future perspectives

As mentioned in **Chapter 1**, the efficacy of surgery over nonoperative treatment for patient suffering from severe chronic LBP and with signs of lumbar degenerative disc disease at the lower lumbar levels, is still under debate.[53-55] Current evidence does indicate the use of a biopsychosocial framework, to guide management for these patients, taking into consideration patients' desires, and behavioural, psychological, and social factors.[56] Treatment should proceed in a stepwise fashion with initial nonpharmacological treatment, including education that supports self-management and resumption of normal activities, (supervised) exercise, and psychological programmes for those with persistent symptoms.[56] Patients who do not respond to these first-line treatments, and who are substantially functionally disabled by pain, should be triaged in a multidisciplinary setting with a standardized intake.[57] A Cochrane systematic review and meta-analysis by Kamper et al. showed that multidisciplinary rehabilitation programmes with coordinated delivery of supervised exercise therapy, cognitive behavioural therapy, and medication are more effective than usual care (care at the discretion and direction of their healthcare provider).[57] The role of minimal interventional therapies for discogenic pain is uncertain.[56]

A systematic review of Lu et al.[58] on steroid therapy (epidural or intradiscal injection), intradiscal methylene blue injection, and ablative therapy for discogenic back pain, identified 10 prospective RCTs with sham or placebo therapy as controls. Results from these studies, favored methylene blue injection and ablative therapy over sham therapy, whereas the findings on steroid therapy were inconclusive. However, after evaluation of the selection criteria utilized in these RCTs, they doubted whether the conclusions can be applied to the general discogenic pain patient population. This lack of external validity becomes more apparent, as more recent studies have not been able to replicate the reported results for methylene blue injections[59] and ablative therapy.[60] Finally, we know from the study from Willems et al.[61] that for chronic low back pain there are no reliable prognostic tests to aid in clinical decision making whether or not patients will benefit from operative treatment.

Fusion of a symptomatic lumbar spinal motion segment is the most commonly used operative treatment for patients with DDD not responding to conservative care.[62] TDR was introduced as an alternative for spinal fusion for patients with symptomatic lumbar DDD. It may be an effective technique for the treatment of a select group of patients

with presumed discogenic back pain and mono-level lumbar DDD, but without osteoporosis, a collapsed disc space, or facet joint degeneration.[63] Much controversy remains on this subject.

In 2016 a Disc Replacement Summit brought together spinal surgeons with experience in lumbar TDR. A modified-Delphi method was employed to determine what consensus existed in terms of the use of lumbar TDR and its future perspectives.[64] It was concluded that in the active patient subpopulation, TDR should be a standard of care for the operative treatment of symptomatic single-level lumbar DDD.[63] The focus during this meeting concerning future perspectives and research, was mainly on appropriate patient selection for surgery[63] and strategies on reimbursement or budget impact of lumbar TDR.[65]

Concerning appropriate patient selection, long-term follow-up studies are indispensable. In contrast to the consensus reported after the abovementioned meeting, stating that younger patients might benefit more from TDR at short term[63]; the current thesis indicates that at the long run, these patients have an increased risk for revision by spinal fusion. An observation confirmed by other long-term follow-up studies.[19] However, it must be noted that it is possible that the elderly were less demanding or surgeons were less inclined to perform revision surgery because of the associated risks.

In terms of financial implications, it is suggested that TDR might be more cost-effective than posterolateral spinal fusion for patient with symptomatic single-level lumbar DDD after two year follow-up.[66] However, this difference was due to the higher reoperation rate in the fusion group (36% of which 28% was attributed to implant removal, as the implant was diagnosed as a pain generator), when compared with the TDR group (10%).[66] Additionally, TDR can only be applied for a specific and narrow subgroup of patients, for whom spinal fusion does not seem inferior to TDR. Consequently, it is hard believing TDR to be more cost-effective when considering that spinal fusion can be applied for a variety of spinal disorders.

Finally, in terms of future perspectives it is important to discuss correct intraoperative positioning of the TDR. Biomechanical studies have demonstrated an increased facet joint pressure and altered loading patterns after TDR.[37-39,67] These forces on the facet joints can potentially be minimized by correct placement (not too far anterior or posterior) of the TDR.[68,69] Furthermore, this thesis indicates in conjunction with other studies that the occurrence of subsidence is associated with the position and relative size of the TDR.[42,43,70,71] These factors can be optimized by the surgeon pre- and intraoperatively. Taking this into account, it is remarkable how little is being published about pre-operative templating or patient-specific implants in TDR, especially when compared to spinal fusion.[72] Only two articles of one study group report on pre-

operative templating using a finite element model, predicting post-operative ROM in 17 patients.[73,74] One biomechanical study investigated the occurrence of subsidence in relation to patient-specific implants in cadaveric vertebrae.[75] If TDR for patients with symptomatic lumbar DDD is here to stay, future research should not only focus on appropriate patient selection, but also on improving correct design and placement of the TDR.

In conclusion, total lumbar disc replacement (TDR) seems a safe procedure with roughly the same reoperation rates as spinal fusion at long-term follow-up and no excessive late complications or revision rates. However, the presumed benefits of TDR over spinal fusion, in terms of residual-mobility and lower occurrence of ASD, seem to diminish over time and do not improve clinical outcome. When considering that TDR is only suitable for a specific subgroup of patients, whereas spinal fusion can be applied for a variety of spinal disorders, TDR has little added value compared to spinal fusion. In those patients diagnosed with a failed TDR, revision by spinal fusion is clinically beneficial in only about half of the cases, and with no benefit from additional TDR removal as compared to posterolateral instrumented fusion alone. Considering revision by instrumented posterior fusion for patients with radiographic subsidence and signs or symptoms, seems a viable option after conservative treatment has failed.

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Valorization

Chronic low back pain (LBP) is one of the most common disabling conditions in Western society, resulting in substantial economic costs related to the utilization of healthcare resources and immense indirect costs by disability and productivity losses. In the Netherlands, it is estimated that the direct health care costs related to back pain exceed 1.3 billion euros. Moreover, the indirect costs of lost productivity due to work absenteeism and early retirement were estimated to be up to ten times higher than the direct costs. Globally, chronic LBP was responsible for 60.1 million disability-adjusted life-years in 2015. The Global Burden of Disease Program was initiated to investigate the worldwide impact of different diseases on health status and disability. For all diseases studied, the highest degree of disability, as measured by patient health status preferences, was found for (chronic) LBP. Moreover, the global burden of chronic LBP is projected to increase even further in coming decades.

Degenerative Disc Disease (DDD) is assumed to be a major cause of LBP and spinal fusion of a symptomatic lumbar spinal motion segment is the most commonly used operative treatment for patients not responding to conservative care. Total disc replacement (TDR) was introduced as an alternative for fusion for these patients. However, the choice of either spinal fusion or TDR remains controversial. For fusion a considerable amount of studies report on long-term clinical outcome. For TDR however, long-term studies are scarce, and spine surgeons should be cautious about performing TDR on a large scale before long-term follow-up studies are available.

In this thesis the long-term complication and revision rates of the SB Charité III TDR were examined. Additionally, an assessment was made to identify risk factors for revision or worse clinical outcome. It was found that the vast majority of reoperations, including revision spinal fusions, occurred in the first 10-years after TDR. This indicates that the occurrence of late complications or reoperations, as seen after total hip replacements, is not applicable for primary TDR. A minimum 10-year follow-up seems sufficient to be able to reliably report on the safety and survival of a TDR implant. Rheumatoid arthritis, osteoporosis, age <45 years at the time of surgery, BMI >30, and previous spinal surgery were all associated with a worse clinical outcome after TDR. The identification of these risk factors may help in decision making and more appropriate patient selection for this procedure, which could help improve clinical outcome and decrease revision rates of future TDR procedures.

TDR has been introduced in order to preserve motion at the affected level and mimic the morphology of the intervertebral disc. Aiming to prevent the occurrence adjacent segment disease (ASD) as seen after lumbar fusion, and thus a presumably better long-term outcome. In the current thesis residual-mobility was noted in only one third of the

patients at last follow-up. No significant associations were observed between residual-mobility and the different patient- or procedure-related characteristics, clinical outcome, or the occurrence of ASD. In addition, ASD and clinical outcome were not related either. This is relevant information in the ongoing debate on optimal treatment modality for DDD, as the presumed benefits of TDR over fusion (i.e. preserving motion and therefore reducing symptomatic ASD) could not be substantiated in this thesis. It seems that not so much the extent of motion, but rather the quality of motion (i.e. more physiological motion) is key.

Subsidence of TDR, defined as the penetration of the prosthetic endplate into the vertebral endplate is a frequently documented complication. It is important to realize that patients with symptoms and radiographic subsidence, even without clear signs of wear or displacement, do undergo revision surgery. However, until now there were no studies describing the relation between subsidence and clinical outcome. The current thesis indicates that there is a significant relation between the occurrence of radiographic subsidence and worse clinical outcome of the patient. Having established this, performing revision surgery for patients with radiographic subsidence and signs or symptoms seems a more viable option. Next, threshold values were obtained to identify patients with symptomatic subsidence. These thresholds can be of assistance to identify patients most likely to benefit from revision surgery for subsidence. Finally, it was determined that the occurrence of symptomatic subsidence can be predicted by incorrect placement or shape mismatch on the direct postoperative radiographs. These are factors that can be optimized by the surgeon, and should be facilitated by future research on improvements in pre-operative templating.
We're currently looking at developing a web-based version of our custom developed and validated software package implemented in Matlab (Matlab R2017b, Mathworks, MA). Doing so, other physicians would be able to use our model to determine whether symptomatic subsidence is likely in their patients, with a presumed failed TDR. In addition, it might be possible to anonymously collect this inserted data to further optimize and validate the current model.

With the introduction of any new medical implant it is important to know how to handle failures. Can the implant be removed safely without major complications, if necessary? If this is not the case, use of such a device should be reconsidered. This thesis indicates that revision by spinal fusion of a failed TDR is clinically beneficial in about half of the patients. No clear benefit from additional TDR removal as compared to posterolateral instrumented fusion alone could be identified. Especially, when considering the substantial complications and costs associated with TDR removal, this should not be advocated routinely.

Summary

Nederlandse Samenvatting

List of Abbreviations

Summary

Lumbar total disc replacement (TDR) has been introduced as an operative treatment for patients with chronic low back pain, not responding to conservative care, based on the hypothesis that chronic low back pain originates from degenerative disc disease. Most commonly, symptomatic lumbar spinal motion segments are fused. However, spinal fusion is associated with negative side effects such as proximal facet-joint violation, decrease in spinal motion, pseudarthrosis, and symptomatic adjacent segment disease (ASD). TDR has also been associated with drawbacks, such as subsidence, dislocation or malposition of the implant, increasing axial rotational instability, and excessive loads to the facet joints. Mid- to long-term studies on this subject are scarce. Therefore, much debate remains on the use and effectiveness of TDR, in particular concerning fear of high rates of late loosening and revisions.

In **Chapter 2**, the long-term clinical outcome in terms of patient satisfaction, complication- and revision rates after TDR were examined. Additionally, an assessment was made to identify risk factors for revision or worse clinical outcome. It was found that after a mean follow-up of almost 20-years, the overall reoperation rate for patients with a lumbar TDR was 31.1% and that in 19.9% revision spinal fusion at the index level had been performed. Most of the revision procedures (81.4%) had occurred in the first 10-years after the TDR. Therefore, fear of excessive late revision procedures following TDR could not be substantiated.
Rheumatoid arthritis, osteoporosis, age <45 years at the time of surgery, Body Mass Index >30, and previous spinal surgery were all significantly associated with worse clinical outcomes in terms of a Visual Analog Scale (VAS) score for pain ≥50 or an Oswestry Disability Index (ODI) score ≥40. Proper patient selection with consideration of the identified risk factors, may help to improve the clinical outcome in patients considered for TDR.

TDR has been introduced in order to preserve motion (residual-mobility) at the affected level, aiming to prevent the occurrence of ASD as seen after lumbar fusion. However, it is uncertain whether these presumed beneficial effects remain. In **Chapter 3,** the long-term occurrence of residual-mobility and ASD after TDR were evaluated. Patients were considered to have ASD, if in one or more adjacent segments of the TDR a severe disc degeneration was observed at last follow-up, or if a significant increase in disc degeneration was observed over time. Residual-mobility was defined as a minimal change of 4.6° in the sagittal alignment angles at the index level of the TDR.
Residual-mobility was noted in one third of the patients at last follow-up (mean 16.7 years). No significant associations were observed between residual-mobility and the different patient- or procedure-related characteristics, clinical outcome, or the occurrence of ASD. In addition, ASD and clinical outcome were not related either.

Randomized controlled trials have shown that the risk of ASD following TDR is significantly lower when compared with spinal fusion at five years follow-up. Similar to our study, the appearance of ASD does not seem to significantly increase revision surgery or deteriorate clinical in these studies. Biomechanical studies have shown that the movement of a TDR differs from that of a normal disc in an intact spine. So maybe not so much the extent of motion, but rather the quality of motion is the main factor in the occurrence of ASD.

Subsidence of TDR, defined as the penetration of the prosthetic endplate into the vertebral endplate, is a frequently documented complication, which may ultimately lead to spontaneous fusion of the vertebral segment or to failure of the TDR. There are no studies describing a clear relationship between radiographic subsidence and symptoms. Nevertheless, patients with subsidence, even without clear signs of wear or displacement, will often undergo revision surgery. A custom developed and validated software package was used in **Chapter 4** to create a 3-dimensional graphical representation of the implant in relation to the bony endplates using the anterior-posterior and lateral radiographs. By projecting the prosthetic endplate on the plane representing the vertebral endplate, the Penetrating Bone Volume (PBV) and the Angular Rotation (AR) could be calculated. Patients were assigned to a success- or failure-group based on their reported VAS- and ODI-scores (failure was defined as VAS ≥50 in combination with an ODI ≥40).
Both the AR and PBV were significantly higher in the failure-group compared to the success-group, at last follow-up. This also applies when the differences between the values at last follow-up and directly post-operative were calculated (ΔAR and ΔPBV). These findings indicate that there is a relation between the occurrence of radiographic subsidence and a worse clinical outcome of the patient. The next step is to identify patients with symptomatic subsidence. Theretofore, ROC-curves were plotted to determine threshold values for the occurrence of failure. Symptomatic subsidence was defined as a PBV at last follow-up of ≥1223 mm^3 or a ΔPBV of ≥829 mm^3. These thresholds can be of assistance to identify patients most likely to benefit from revision surgery for subsidence. Finally, it was determined that both an AR ≥4^o directly postoperative or a coverage of the vertebral endplate by the TDR endplate of less than 50%, are associated with the occurrence of symptomatic subsidence at last follow-up. These are factors that can be optimized by the surgeon pre- or intraoperatively.

It has been suggested that when the TDR has subsided or mechanically failed, TDR removal should be considered. Nevertheless, there is an ongoing discussion whether revision surgery for failed TDR is beneficial, and if so, what the optimal revision strategy should be. As yet, little is known about the long-term effects of posterolateral instrumented fusion combined with TDR removal or fusion alone. **In Chapter 5** the long-term clinical results (minimum follow-up of 5-years) and complications of these two

revision strategies for patients with a failed TDR were compared. TDRs were removed in case of evident malposition or migration, and in case of a strong patient desire for removal.
At last follow-up, a minimally clinically important difference (MCID) in VAS- and ODI-score was found in 62.5% and 43.8 % in the removal group, and in 43.5% and 39.1 % in the fusion group, respectively. The small differences in MCID were not statistically significant nor clinically relevant. The percentage of (late) re-operations for complications such as pseudarthrosis, were comparable for both revision procedures. In conclusion, no clear benefit from additional TDR removal as compared to posterolateral instrumented fusion alone could be identified. Additionally, it should be stressed that TDR removal is associated with considerable intra-operative complications such as major vessel bleeding or intestinal injury.

Nederlandse samenvatting

De lumbale totale discus prothese (TDR) werd geïntroduceerd als een operatieve behandeling voor patiënten met chronische lage rugpijn in verband met degeneratie van de tussenwervelschijf (discus intervertebralis), waarbij conservatieve therapie onvoldoende soelaas heeft gebracht. In de meeste gevallen wordt het verondersteld pijnlijke lumbale bewegingssegment namelijk vastgezet, maar deze operatieve ingreep (spondylodese) is geassocieerd met beschadiging van de aangrenzende facetgewrichten, afname van de lumbale mobiliteit, pseudartrose en slijtage van de aangrenzende bewegingssegmenten (Adjacent Segment Disease, ASD). Een TDR werd hiervoor als oplossing gezien, maar heeft ook een aantal nadelen zoals het wegzakken van het implantaat in het wervellichaam (subsidence), het luxeren of migreren van de TDR en een toename van de belasting op de facetgewrichten. Er zijn maar weinig studies beschikbaar met een middellange- tot lange follow-up duur van de TDR. Hierdoor blijft er veel discussie bestaan of TDRs veilig gebruikt kunnen worden, voornamelijk met betrekking tot een mogelijke grote toename van revisies op de langere termijn.

Hoofstuk 2 beschrijft de lange termijn resultaten van de TDR, wat betreft patiënt tevredenheid, complicaties en revisiepercentages. Daarnaast werden er risicofactoren geïdentificeerd voor een verhoogde kans op een revisie of een slechtere klinische uitkomst. Het totale percentage heroperaties voor patiënten met een TDR betrof 31,1% na een gemiddelde follow-up van bijna 20 jaar. In 19,9% van de patiënten werd een revisie van de TDR middels een spondylodese uitgevoerd. Het overgrote deel van deze procedures (81,4%) gebeurde in de eerste 10 jaar na de initiële TDR. De angst voor een grote toename van late revisies lijkt hiermee ongegrond.
Reumatoïde artritis, osteoporose, leeftijd <45 jaar ten tijde van de TDR, Body Mass Index >30 en eerdere spinale chirurgie werden geassocieerd met een significant slechter klinische uitkomt, gedefinieerd als een pijnscore op de visuele analoge schaal (VAS) ≥50 of een score van ≥40 op de Oswestry Disability Index (ODI). Een optimalisering in patiëntselectie kan de klinische uitkomst helpen verbeteren voor toekomstige patiënten die mogelijk in aanmerking komen voor een TDR.

TDR werd geïntroduceerd als alternatief voor een spondylodese, met als doel de beweeglijkheid op het aangedane lumbale niveau te behouden en zodoende de incidentie van ASD te reduceren. Het is echter onduidelijk of deze veronderstelde gunstige effecten op de langere termijn blijven bestaan. In hoofdstuk 3 wordt de mate van beweeglijkheid en de incidentie van ASD na een TDR geanalyseerd. ASD werd bij patiënten vastgesteld indien er ten tijde van de laatste follow-up, in één van de aangrenzende bewegingssegmenten van de TDR een ernstige degeneratie van de discus werd waargenomen, of als na verloop van tijd een significante toename van

discusdegeneratie zichtbaar was. Het behoud van beweeglijkheid werd gedefinieerd als een minimale sagittale mobiliteit van 4,6° op het niveau van de TDR.
Het behoud van beweeglijkheid werd ten tijde van de laatste follow-up (gemiddeld 16,7 jaar) bij één derde van de patiënten opgemerkt. Er werden geen significante associaties waargenomen tussen behoud van beweeglijkheid, de verschillende patiënt-karakteristieken, klinische uitkomst of het optreden van ASD. Daarnaast was klinische uitkomst ook niet gerelateerd aan de aanwezigheid van ASD. Gerandomiseerde trials hebben aangetoond dat het risico op ASD na vijf jaar follow-up significant lager is voor een TDR vergeleken met een spondylodese. In overeenstemming met onze studie, lijkt deze observatie echter niet te leiden tot een significant verschil in klinische uitkomst of het percentage revisies. Daarnaast hebben biomechanische studies aangetoond dat het bewegingspatroon van een TDR verschilt van dat van een normale discus in een intacte wervelkolom. Kortom, niet zozeer de mate van beweeglijkheid, maar eerder de kwaliteit van de beweging is vermoedelijk de belangrijkste factor bij het optreden van symptomatische ASD.

Subsidence van de TDR is een veelvoorkomende complicatie en kan uiteindelijk leiden tot ankylose van het bewegingssegment of tot het falen van de TDR. Hoewel er geen studies zijn die een duidelijk verband beschrijven tussen radiologische subsidence en symptomen, ondergaan patiënten hiervoor in de praktijk met regelmaat revisiechirurgie. In hoofdstuk 4 werd een gevalideerd model toegepast om op de postero-anterieure en laterale röntgenfoto's een driedimensionale grafische weergave van de TDR te creëren. Door de eindplaat van de TDR te projecteren op het vlak van de eindplaat van het wervellichaam, konden de mate van subsidence (‘Penetrating Bone Volume’, PBV) en de rotatiehoeken (‘Angular Rotation’, AR) worden berekend. Patiënten werden toegewezen aan een succes- of faalgroep op basis van hun gerapporteerde VAS- en ODI-score (falen werd gedefinieerd als een VAS ≥50 in combinatie met een ODI ≥40).
Zowel de AR als de PBV waren significant hoger in de faalgroep in vergelijking met de succesgroep ten tijde van de laatste follow-up. Dit was ook het geval wanneer de verschillen tussen de waarden op de laatste follow-up en direct-post-operatief werden berekend (ΔAR en ΔPBV). Deze bevindingen suggereren dat er een verband bestaat tussen het optreden van radiologische subsidence en een slechtere klinische uitkomst voor de patiënt. De volgende stap is het identificeren van patiënten met symptomatische subsidence. Hiervoor werden ROC-curves toegepast om drempel-waarden te bepalen voor het optreden van falen. Symptomatische subsidence werd zodoende gedefinieerd als een PBV bij de laatste follow-up van ≥1223 mm^3 of een ΔPBV van ≥829 mm^3. Deze drempelwaarden kunnen behulpzaam zijn bij het voorspellen welke patiënten mogelijk het meest gebaat zullen zijn bij een revisie wegens subsidence. Daarnaast werd vastgesteld dat een AR ≥4° direct-postoperatief, en een contactoppervlak tussen de eindplaat van de TDR en het wervellichaam kleiner dan 50%, beide voorspellend zijn voor het optreden van symptomatische subsidence ten tijde van

de laatste follow-up. Deze factoren kunnen perioperatief door de chirurg geoptimaliseerd worden.

Er wordt gesuggereerd dat wanneer er sprake is van subsidence of mechanisch falen van een TDR, serieus moet worden overwogen om deze te verwijderen. Niettemin blijft er veel discussie bestaan of revisiechirurgie voor een gefaalde TDR bevorderlijk is, en zo ja, wat de optimale revisie-strategie dan zou moeten zijn. Tot op heden is er weinig bekend over de lange termijneffecten van een posterolaterale spondylodese in combinatie met het verwijderen van de TDR versus alleen een posterolaterale spondylodese. In Hoofdstuk 5 werden de klinische resultaten en complicaties van deze twee revisiesstrategieën voor patiënten met een gefaalde TDR vergeleken na een minimale follow-up van 5 jaar. Een TDR werd verwijderd bij evidente malpositie of migratie of indien er sprake was van een nadrukkelijke wens van de patiënt.
Ten tijde van de laatste follow-up, werd een minimaal klinisch relevant verschil (MCID) in VAS- en ODI-scores gezien bij respectievelijk 62,5% en 43,8% van de patiënten waarbij de TDR ook werd verwijderd, en bij 43,5% en 39,1% in de groep waarbij alleen een spondylodese plaatsvond. Deze verschillen in MCID waren statistisch niet significant noch klinisch relevant. Het percentage (late) heroperaties voor complicaties zoals pseudartrose waren vergelijkbaar voor beide procedures. Het verwijderen van de TDR lijkt dus niet bevorderlijk, des te meer als we de substantiële complicaties die hiermee gepaard gaan, zoals bloedingen van de grote vaten en darmperforaties, hierbij in beschouwing nemen.

List of abbreviations

AP	Antero-posterior
AR	Angular Rotation
ASD	Adjacent Segment Disease
AUC	Area Under the Curve
AUI	Areal Undersizing Index
BMI	Body Mass Index
CI	Confidence Intervals
DDD	Degenerative Disc Disease
DEXA	Dual-energy X-ray absorptiometry
DPO	Direct-postoperative
EQ-5D	EuroQol-5D
FDA	Food and Drug Administration
FJA	Facet Joint Arthropathy
FJD	Facet Joint Degeneration
HR	Hazard Ratios
IA	Implant Asymmetry
ICC	Interclass Correlation Coefficient
LBP	Low Back Pain
LFU	Latest Follow-up
MCID	Minimally Clinically Important Difference
MEC	Medical Ethics Committee
ODI	Oswestry Disability Index
OR	Odd Ratio
PBV	Penetrated Bone Volume
PI	Pelvic Incidence
PROM	Patient Reported Outcome Measures
RA	Rheumatoid Arthritis
RCT	Randomized Controlled Trial
ROC	Receiver Operating Characteristic
ROM	Range of Motion
SD	Standard Deviation
SEM	Standard Error of the Mean
SF-36	Short Form-36
TDR	Total Disc Replacement
THR	Total Hip Replacement
UHMWPE	Ultra High Molecular Weight Polyethylene
VAS	Visual Analog Scale

Dankwoord

Curriculum Vitae

Publications

Dankwoord

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Curriculum Vitae

Joep Kitzen was born in Schiedam, the Netherlands, on November 10th, 1986. He is the eldest child to Ger and Janine, and brother to Jessie. After high school graduation at the Candea College in Duiven in 2005, he started medical school at the Maastricht University. In July 2011, Joep completed his medical degree and started working as a resident (non-training) at the Department of Orthopaedic Surgery, Orbis Medical Centre in Sittard (supervision: dr. N.P. Kort). His specialist orthopeadic training started in 2014 at the Department of General Surgery, Zuyderland Medical Centre in Heerlen (supervision: dr. M.N. Sosef).

During his residency he developed the ambition to further improve his research skills and obtain a PhD degree. In 2014 this resulted in the collaboration between the Maastricht University Medical Centre (MUMC+) and the Zuyderland Medical Centre on the research described in this thesis (supervision: prof. dr. P.C. Willems, prof. dr. L.W. van Rhijn, and dr. N.P. Kort).

In 2015 he continued his residency at the Maxima Medical Centre in Eindhoven and Veldhoven (supervision: dr. J.B.A. van Mourik), and in 2016 at the MUMC+ (supervision: dr. H. Staal). In 2018 he returned to the Maxima Medical Centre (supervision dr. R.P.A. Janssen) for the remaining two years of his training. During his final six months, he had the opportunity to further specialise in spinal surgery at the University Medical Centre in Utrecht, the Netherlands (supervision: dr. J.J. Verlaan and prof. dr. F.C. Öner).

In July 2020 he commenced a fellowship in Orthopaedic Trauma at the Foothills Medical Centre in Calgary, Canada, under the supervision of dr. P.J. Duffy and dr. R.E. Buckley. Joep lives with his wife Susanne van Voorst Vader and their daughter Floor (2019).

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