Failure mechanisms of the lumbar total disc prosthesis

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CHAPTER 1

General introduction

For patients who suffer from degenerative disc disease (DDD) of the lumbar spine, replacement of the affected disc can be considered as a surgical option. A total disc replacement (TDR) aims to reduce pain and to maintain the motion of the spinal segment. However, knowledge regarding the long term characteristics and success of this implant is insufficient.

In this thesis mid- and long-term sequelae of a TDR, such as subsidence and periprosthetic tissue reactions are studied. In addition, the surgical techniques of TDR removal revision surgery, and clinical outcomes of two revision strategies for patients with a failed TDR implantation are described.

LOW BACK PAIN

Low back pain (LBP) is a major health problem in the modern Western societies. The life-time prevalence of LBP is 50-80%, with one third seeking medical care for their disabling pain.¹⁻⁴ In the Netherlands, it was estimated that the direct health care costs related to back pain exceed 700 million Euros.⁵ Moreover, the indirect costs, including disability and early retirement, are estimated ten times higher than the direct costs.⁶

For patients with LBP, an active lifestyle and use of pain medication (e.g. analgesics or non-steroidal anti-inflammatory drugs) is advised in the first phase. After three months, a combination of pain management and physical therapy can be considered. If a prolonged period of structured conservative treatment fails, surgical treatment can be considered.⁷ Several surgical techniques have been developed to treat degeneration of the intervertebral disc, often called 'degenerative disc disease' (DDD). Spinal fusion is still considered as the 'golden standard' of surgical treatment of DDD, however, total disc replacement (TDR) is an increasingly used alternative surgical method.

HISTORY OF TOTAL DISC REPLACEMENT

In the early 1960s Fernström described the first clinical trial of an intervertebral disc prosthesis, in which a stainless steel ball was used to replace the intervertebral disc (Figure 1.1).⁸⁻¹⁰ The ball was intended to maintain disc space height as well as lumbar motion. Although Fernström reported reasonable to good short-term outcomes,¹⁰ long-term clinical results were unsuccessful because of subsidence of the implant into the bony end plates, loss of disc height and the recurrence of LBP.⁸⁻¹² Nevertheless, Fernström introduced the notion that a motion-preserving disc replacement, possibly might avoid complications (e.g. adjacent degeneration, pseudo-arthritis) that could occur after spinal fusion. Since then, multiple TDR devices have been designed for use

in the lumbar spine, although the majority of them has never been implanted in humans.^{10,13-15}

The AcroFlex artificial disc, an elastic TDR model was designed by Steffee, consisted of two porous coated metallic endplates fused to a polyolefin-based rubber core, that was implanted in a series of patients.^{8,9,11,16,17} However, 16 complications were observed, and in two out of 28 patients osteolysis and loosening at the bone-implant interface was found. They highlighted the potential problem of wear particles leading to osteolysis and the discrepancy between biomechanical testing and *in vivo* results.^{16,17} Despite the high number of failures which lead to withdrawal of the device from the market, the concept of shock absorption while maintaining spinal motion represented a step forward in the development of current TDR designs.⁸

Figure 1.1 Fernströms stainless steel ball prosthesis, with A) lateral and B) anterior-posterior radiographs.^{12,14}

INDICATIONS AND AIMS FOR TDR

Indications for a TDR are symptomatic DDD confirmed by CT or MRI scans. DDD was defined as discogenic back pain with degeneration of the disc confirmed by patient history and radiographic studies, including one of the following factors: contained herniated nucleus pulposus, little or no facet joint degeneration changes, decreased intervertebral disc height (≥ 4 mm) and/or scarring or thickening of the annulus fibrosis with osteophytes. Contra-indications for TDR are spondylolysis, spondylolisthesis, osteoporosis, infections, bony lumbar stenosis, metabolic bone disease, implant material allergy, morbid obesity, scoliosis, and spinal tumor.^{15,18-20}

The current generation TDRs are designed to: *i*) restore and maintain a near normal intervertebral disc space, lordosis and instantaneous axis of rotation, *ii*) achieve (near) normal range of motion, and *iii*) to restore pain-free motion, as well as the load-carrying capacity of a diseased functional spinal unit.^{9,14,21,22} Furthermore, long-term durability and stability are essential to maintain motion, and to prevent adjacent segment degeneration.

SB CHARITÉ III TDR

The SB Charité III TDR (Waldemar Link, Germany; DePuy Spine, Raynham, MA) was the first artificial disc that was implanted on a large scale.^{13,23} It was designed by Shellnack and Büttner-Janzen,^{20,22,23} who aimed to replicate the kinematics of a vertebral disc. They adopted the 'low friction' principle of ultra-high molecular weight polyethylene (UHMWPE)-on-metal articulation, as introduced by Sir John Charnley when creating the first successful hip prosthesis.^{12,21,23} The Charité TDR consists of a bi-convex sliding UHMWPE core that acts as a mobile core, which articulates against two concave cobalt-chrome-molybdenum (CoCrMo) endplates. A radiopaque wire is positioned around the UHMWPE core for radiographic localization of the core. Six teeth are implanted on the endplates for fixation into the bony vertebral endplate (Figure 1.2). The SB Charité III TDR was launched internationally in 1989, starting in the Netherlands and France. The Food and Drug Administration (FDA) approved the use of the SB Charité TDR for clinical practice in the USA in 2004.^{15,21}

Figure 1.2 **A)** SB Charité III TDR¹³, **B)** Anterior-posterior and lateral radiographs of the Charité TDR implanted in the lumbar (L4-L5) spine.

Since its introduction, there have been a number of changes in the Charité TDR design to improve the durability. The first change was in 1997, when the sterilization and packaging process of the UHMWPE cores was changed, with the aim to obtain improved wear and strength performance with minimal oxidative degeneration. Before, the Charité UHMWPE cores were fabricated from compression molded GUR

412 resin, packed in air and gamma sterilized in air; whereas from 1997, UHMWPE cores are sterilized in an inert nitrogen/vacuum environment (N-VAC), and the UHMWPE core material was changed to compression molded GUR 1020.^{21,24} A second change, that was introduced in 1998, was the introduction of bioactive hydroxyapatite coated endplates to initiate bony ingrowth, thereby providing resistance for migration of the TDR. Furthermore, in 2004, the packaging of the UHMWPE was changed from a polymeric barrier packaging N-VAC to a foil pouch (GVF) barrier packaging.²¹

RESULTS AFTER TDR

Complications and reoperations

Recently, van den Eerenbeemt et al.²⁵ and Yajun et al.²⁶ reviewed the effectiveness and safety of the SB Charité III TDR. These review studies identified a low quality of evidence supporting the effectiveness of the Charité TDR over spinal fusion, although the long-term effectiveness of this relatively new medical device compared to spinal fusion remains unclear.²⁵⁻²⁸ Short-term follow-up studies reported fair to good results.²⁹⁻³² A 10-year follow-up study demonstrated that 90% of the patients who received a TDR had good to excellent clinical outcomes.³¹ The FDA study, in which the Charité TDR was tested for approval in the USA, showed an overall clinical success rate of 57.1% and 57.8% after two and five year follow-up respectively.^{13,33,34} At 5 year follow-up, there were no differences in safety and clinical outcomes after spinal fusion as compared to TDR.³³ This study reported that between 2 and 5 year follow-up, device failures were observed in the TDR group only (2.2%).³³ However, 25% of the patients from the initial study were not available in the 5 year follow-up study, because 6 out of the 14 initial sites declined to participate.³³ Putzier et al.²⁷ found similar results for TDR and spinal fusion with an average follow-up of 17 years. Although the life-time of a TDR implant should be minimal 40 years due to the young age at implantation, the long-term durability of a TDR is still uncertain.^{27,35-39}

Most cohort studies reported a wide range in number of complications (10-40%) after TDR implantation.²⁵ These complications are related to surgical approach (e.g. vascular or neurological damage, retrograde ejaculation), prosthesis (e.g. subsidence, migration, facet joint degeneration, UHMWPE wear, adjacent level degeneration) or treatment (e.g. recurrent back and/or leg pain).^{25,27,31,40-42} Some of these complications warrant the need for surgical revision strategies.⁴³ The reported number of reoperations varies between two and 14% for the Charité TDR design.^{13,25,26,40,44,45}

Wear debris and inflammatory response

UHMWPE wear debris is a well known phenomenon in total hip and knee arthroplasty (THA, TKA respectively) that may ultimately lead to failure of the prosthesis, due to osteolysis and aseptic loosening. A clinically loose THA or TKA can lead to pain and instability, necessitating revision surgery.⁴⁶⁻⁴⁸ UHMWPE surfaces generate large numbers of wear particles which cause periprosthetic inflammatory reactions.^{49,50} It was assumed that UHMWPE wear would not be a clinically relevant topic in TDR,^{23,51} based on the idea that the intervertebral disc is not a synovial joint, and that the motion between the lower lumbar segments is limited as compared to THA or TKA.²³ However, in a few studies, cases of periprosthetic osteolysis potentially attributable to UHMWPE wear debris after TDR have been reported.^{17,45,52,53} These studies have shown that UHMWPE wear and inflammatory reactions are present after lumbar disc arthroplasty and can be a clinical issue of concern.

RATIONALE AND AIM OF THIS RESEARCH

The state of knowledge regarding the clinical outcome of lumbar TDRs has evolved rapidly, however, the long-term clinical success of the SB Charité III TDR is still unknown. As explained above, the broad range of outcomes in literature raises questions about the long-term success of motion preservation, inflammatory reactions and wear particle generation with this type of UHMWPE-on-metal implant. Based on the clinical experiences of UHMWPE in total hip and knee arthroplasty, the production of wear is a clinical concern. Wear debris induced osteolysis has been implicated as a potential mechanism for late onset failure.

Research questions addressed in this thesis are:

- Are TDR devices safe and durable or is wear debris, as we see in total joint replacement elsewhere in the body, a matter of clinical concern?
- Is there an acceptable and safe procedure in case of TDR failure? Can the device, if necessary, be removed without major complaints?

This study contributes to the knowledge of the implantation of a new lumbar spinal device, by considering the consequences of TDR implantation and evaluating treatment options in failed TDRs. The adherence to great vessels and the nerve plexus, causes a substantial operative risk when performing revision surgery. Posterolateral instrumented fusion or TDR removal with anterior interbody fusion followed by posterolateral instrumented fusion are studied in this thesis. Additionally, we designed a method to assess and classify the presence of subsidence of the TDR implant into the vertebral endplate, and studied whether undersizing of the TDR was related to subsidence. Finally, we analyzed periprosthetic tissue samples obtained

during TDR revision surgery to study the occurrence of inflammatory reactions and (sub)micron wear debris in the lumbar spine.

OUTLINE OF THE THESIS

This thesis begins with a description of the surgical technique to remove a TDR and the occurrence of complications in this kind of surgery (chapter 2). Chapter 3 and 4 concerns the clinical results of two types of revision strategies of the SB Charité III TDR, after short- and mid-term follow-up respectively. Chapter 5 described a reliable method to measure subsidence of the TDR in the bony endplate of the vertebrae and the consequences of undersizing of the TDR. The next three chapters focus on tissue reactions that are observed after revision surgery. The observed periprosthetic inflammatory tissue reactions and wear analysis after TDR are presented in chapter 6 and compared to hip and knee arthroplasty reactions in chapter 7. Chapter 8 focuses on the submicron-sized wear particle analysis. Finally, chapter 9 of this thesis will discuss the main findings and implications of TDR in the lumbar spine.

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CHAPTER 2

Removal of the Charité lumbar artificial disc prosthesis Surgical technique

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J Spinal Disord Tech. 2009;22:334-9

ABSTRACT

Study Design

Descriptive study of a surgical technique for removal of the Charité total lumbar disc prosthesis.

Objective

To describe the surgical technique to remove a total disc prosthesis and the occurrence of complications in disc removal surgery.

Summary of background data

As lumbar total disc replacement seems to be more and more an accepted option to treat degenerative disc disease, the more will the need for removal increase in case of failure.

Methods

Twenty-nine Charité total disc prostheses were removed in 25 consecutive patients. To avoid mobilization of the adhered great vessels away from the spine, we address L4-L5 (or higher) anterolaterally from the left side, after mobilizing the psoas and exposing the lateral side of the disc level with the prosthesis. The approach to L5-S1 is similar to the implantation of the disc prosthesis. After removal of the prosthesis, the created defect is filled with a bone graft to accomplish an anterior fusion. This retrieval surgery is always combined with a posterior pedicle screw fusion.

Results

In our series, we had 4 intraoperative major vessel lesions without major blood loss; 1 of these cases developed a deep venous thrombosis of the left leg. In 1 case, we encountered a small colon lesion and in 1 patient, a lesion of the ureter resulting in resection of the kidney. In 1 case, we had profound bleeding from the bone beneath an S1 endplate, which resulted in a total blood loss of 5100 ml. In another patient, we planned to remove the disc prosthesis; however, because of rupture of the small intestine only posterior fusion was performed.

Conclusions

Retrieval of a Charité artificial disc prosthesis is feasible, but it has its inherent risks.

INTRODUCTION

Symptomatic lumbar degenerative disc disease is a challenging entity to treat. As an alternative to spinal fusion, total disc replacement (TDR) surgery is more and more becoming an accepted treatment for patients with degenerative disc disease. In theory, such a procedure has many advantages over spinal fusion, as it is intended to preserve motion and may reduce adjacent level degeneration.^{1,2}

But, as in all kind of implant surgeries, failures can make revision surgery a necessity. McAfee et al.³ report 8.8% revision procedures at the index level. Retrieval of artificial discs is prone for complications.⁴ The specific risks of the anterior surgical approach to the spine are larger in revision surgery. For example, visceral injury occurs more easily owing to scarring of previous retroperitoneal surgery. Mostly, these lesions can be easily repaired by simple suturing. Owing to adhesions, vessels are more fragile and adherent to the spine. As the great vessels are located anterior to the discs at levels above L5–S1 and the bifurcation of the aorta and vena cava mostly lies directly superior to the L5–S1 disc, vascular complications are the most feared.^{5–7} McAfee et al.³ report a 3.6% incidence of vessel injury in primary TDR and 16.7% in anterior revision surgery. Ready availability of a vascular surgeon is essential in this kind of surgery. Other potential serious complications are ureteral injury and damage of the neural prevertebral plexus which in male patients can lead to retrograde ejaculation, loss of libido, and even impotence.^{8,9}

Indication for revision surgery is persistent severe low back pain and/or leg pain. The cause for this pain can be implant related, whether or not owing to malpositioning, with prosthesis (sub)luxation, migration, subsidence, and breakage of the metal ring of the core or wear. Secondary facet degeneration or adjacent degeneration can also be the cause of recurrent low back pain after TDR.^{3,4,8,10,11}

We report on 25 consecutive patients in whom we removed 29 Charité artificial disc prostheses at the University Hospital Maastricht, the Netherlands, a tertiary university referral center for spine patients.

The aim of the present study is to describe the surgical technique for removal of the prosthesis and the occurrence of complications in disc removal surgery.

MATERIALS AND METHODS

In the last 5 years, from 2002 up till 2007, we removed 29 Charité artificial disc prostheses in 25 patients with persisting back problems. These prostheses were implanted elsewhere in the period between the years 1989 and 2003. Eighteen patients were female and 7 were male. In this group, the average age at implantation of the disc prosthesis was 41.4 years (range: 33 to 56 y). The disc prostheses were removed on average 8.9 years (range: 3 to 16 y) after implantation. Eighteen patients had prosthesis at a single level: 12 at level L4–L5, 5 at L5–S1, and 1 at L3–L4. Five

patients received disc prosthesis at both L4-L5 and L5-S1, and 1 patient on both L3-L4 and L5-S1. In 2 of these patients, the prosthesis L5-S1 had already been removed elsewhere, leaving L3-L4 or L4-L5 *in situ*. One patient had 3 levels replaced (L2-L3, L4-L5, L5-S1); in this patient, we removed L2-L3 and L4-L5 and left L5-S1 *in situ* because a solid posterior fusion was present at this level.

In another patient, we planned to remove the disc prosthesis on level L5-S1; however, we decided to perform only a posterior fusion because of rupture of the small intestine during the access phase.

The primary indication for removal is persisting severe back pain, and in our group, this was always combined with leg pain.

Radiographic evaluation showed an anterior or lateral malposition of the prosthesis in 3 cases. In 5 cases, there was an anterior migration of the prosthesis. Malsizing (too small) was seen in 6 cases. Subsidence whether or not owing to malpositioning or malsizing was seen in 18 cases. Two cases also had a subluxation of the polyethylene core. Breakage of the metal marker ring was seen in 7 TDRs. In 4 cases, the prosthesis had a good position and size without signs of migration (Table 2.1).

To visualize the position of the great vessels in relation to the spinal column and the prosthesis, we always perform a computed tomography angiography before the surgery (Figure 2.1).

Figure 2.1 CT angiography visualising the common iliac arteries in relation to the spinal column and the total disc prosthesis L5-S1. CT indicates computed tomography. See page 164 for colour figure.

Table 2.1 Characteristics of the patients

Case	Gender	Level	Year TDR	Age at TDR	Endplates coated	TDR in situ (years)	TDR position	Approach	Approach retrieval	Complications	Bloodloss (cc)	Duration retrieval (min)
1	f	L4-5	1991	39	no	11	AM	lumbotomy	lateral		600	160
2	f	L5-S1	1995	39	no	9	S	extension of Pfannenstiel	anterior	lesion left common iliac vein	600	170
3	m	L4-5	1998	46	no	6	TS,S	lumbotomy	lateral		250	125
4	f	L2-3	1992	32	no	12	SL,S,B	lumbotomy	lateral		300	175
5	f	L4-5	1992	32	no	12	MP,AM,B		lateral			
6	m	L5-S1	1998	45	no	7	S,B	lumbotomy	anterior		250	165
7	f	L4-5	2001	47	yes	4	TS,S	lumbotomy	lateral		1000	200
8	m	L4-5	1999	34	yes	6	S	lumbotomy (transperitoneal)	lateral	small colon lesion	450	140
9	f	L5-S1	1997	34	no	8	MP,TS	lumbotomy	lateral		250	150
10	f	L4-5	2002	37	yes	3	G	pfannenstiel	anterior		350	135
		L5-S1	2002	37	yes	3	S	extended lumbotomy	lateral	lesion left common iliac vein	1000	195
									anterior	(2x), DVT left leg		
11	f	L3-4	1992	33	no	13	AM,S,SL	lumbotomy	lateral		350	130
12	m	L4-5	1992	37	no	13	S,B	lumbotomy	lateral		300	135
13	m	L4-5	1989	44	no	16	S	lumbotomy	lateral	lesion left common iliac artery	700	135
14	f	L4-5	1999	46	yes	6	G,B	extended lumbotomy	lateral		5100	250
		L5-S1	1999	46	yes	6	S,B		anterior	epidural plexus and vertebral bone bleeding		
15	f	L4-5	1995	33	no	11	S	lumbotomy	lateral		200	145
16	f	L4-5	1990	55	no	16	MP,AM	lumbotomy	lateral		200	155
17	f	L4-5	2002	43	yes	4	S	extended lumbotomy	lateral		150	190
18	f	L5-S1	2002	43	yes	4	G		anterior			
19	f	L4-5	2001	46	yes	5	TS	lumbotomy	lateral		60	85
20	f	L5-S1	2001	40	yes	4	TS	pfannenstiel	anterior		200	135
21	f	L4-5	2000	42	no	6	G	lumbotomy	lateral		110	90
22	f	L4-5	1993	41	no	13	S,B	lumbotomy	lateral		150	120
		L4-5	1996	42	no	10	AM	lumbotomy	lateral	Due to position veins, L5-S1 prosthesis not accessible, no removal performed	150	180
23	f	L3-4	2003	48	yes	4	S	lumbotomy	lateral		200	130
24	m	L4-5	1998	42	no	9	S	lumbotomy	lateral	lesion left common iliac artery, lesion ureter	500	130
25	m	L5-S1	1991	51	no	16	TS,S	pfannenstiel	anterior		100	165

AM: anterior migration; MP: malpositioned; S: subsidence; SL: subluxation; TS: too small; B: broken metal ring; G: good size and position; DVT: deep venous thrombosis

Surgical Technique

Patient Positioning

The patient is placed under general anesthesia. A Foley catheter is inserted to decompress the bladder. For L4-L5 disc retrieval, the patient is positioned in a semilateral decubitus position, about 30 to 40 degrees, with the left side up using a cushion under the left buttock. An extra support on the right side can be used to prevent the patient from falling off or shifting during the operation.

The supine position is also used when only L5-S1 is addressed. At this level, the intervertebral space is approached from anterior. If fluoroscopy might be needed to identify the level to be operated on, special care is taken to position the patient in a manner that allows proper C-arm movement over and around the operative level.

Surgical approach

It is strongly recommended that the approach be performed by a vascular or access surgeon together with the spinal surgeon, because of potential retroperitoneal scarring and vascular complications that might occur which can be addressed immediately.

There are a number of options with respect to the approach and incision location. In general, we use a laterally extended approach, mostly a lumbotomy (as described below). In 4 cases, we used a Pfannenstiel incision to remove the disc prosthesis at the level L5-S1. When disc prosthesis at the level L4-L5 (or higher) has to be removed, we always use the lumbotomy because of the lateral approach to these levels. In case of retrieval of both L4-L5 and L5-S1, the lumbotomy is somewhat extended distally.

The lumbotomy incision runs somewhat oblique above the left iliac crest (Figure 2.2). The sheath of the oblique abdominal muscles is identified. The 3 layers of oblique and transverse abdominal muscles are transected. Care is taken to ensure the structural integrity of the peritoneal membrane. This is followed by blunt dissection of the peritoneal sac away from the abdominal wall. Scarring makes the peritoneal membrane very fragile and easily perforated. Simple suturing will repair these lesions. In 1 case (L4-L5), we had to go transperitoneal because of the difficult retroperitoneal approach owing to scarring and the very thin peritoneal membrane.

The approach to address L4-L5, L3-L4, or L2-L3 is from the lateral side to prevent mobilization of the aorta and vena cava. Because of previous surgery, these vessels will be adherent to the spine and are at risk for lesions and subsequent major bleeding. First, the psoas muscle is exposed and an abdominal retraction system is placed according to surgeon's preference. Then the L4-L5 (or higher) disc space is approached laterally over the psoas muscle. Care is taken to prevent damage to the ureter that is swept medially together with the peritoneal sac. After reaching the index disc level, the psoas muscle is dissected from the spine and retracted away using the Omnitract (Jordan Medical) table mounted retraction system (Figure 2.2) to

obtain the required lateral approach to L4-L5 (or higher). The great vessels are kept anteriorly and remain untouched. Care is taken not to put too much retraction on the psoas muscle, as this can induce left leg pain and numbness because of stretching of nerves running in the psoas muscle.

Level L5-S1 is addressed anteriorly with the same approach as the implantation of the prosthesis. L5-S1 is situated caudal to the aortic bifurcation and is reached by dissection over the psoas muscle and the left iliac vessels. Again, care is taken to prevent damage to the ureter. The abdominal retraction system is placed to retract the peritoneal sac medially, and further dissection is performed to expose L5-S1. Mobilization of the iliac vessels needs great care because of possible adhesions and scar tissue because of previous surgery. This especially accounts for the left common iliac vein as this often runs across the prosthesis at the L5-S1 level. Careful use of cautery is advised to minimize the risks of retrograde ejaculation, impotency, and vaginal numbness owing to damage of the hypogastric plexus.

Figure 2.2 Intra-operative view of the semi-lateral decubitus position, lumbotomy and Omnitract[®] retraction system. See page 164 for colour figure.

After exposure, the surgeons use the Omnitract system to give a wide and stable exposure. Retractor pins can also be used in the exposure, but are regarded as more dangerous compared with the retractor system. Slippage of these pins is possible and, in fact, created a left common iliac vein laceration in the second operated patient.

With clear visibility of the level operated on, overlying fibrous tissue is cautiously excised. Overlying bone, owing to bony overgrowth or subsidence of the prosthesis into the vertebral body, is carefully removed by using a chisel or osteotome and rongeurs. To remove the prosthesis, we first free 1 of the endplates, including the

teeth of the endplate, by chiseling away some bone (Figure 2.3). The endplate is gripped with clamping forceps and is removed by twisting and pulling maneuvers. The TiCaP porous coated endplates (11 of 29 in our series) are a little more difficult to remove than the ones that are not coated owing to more stable fixation. However osseointegration of bone into the coating was never observed in our series. After removal of 1 of the endplates is accomplished, it is easy to remove the other components of the prosthesis. Alternatively, a spreader system can be used to distract the endplates to remove the sliding core first, but this procedure often requires more space than is available at the level of the prosthesis.

Figure 2.3 Intra-operative view of the anteriorly exposed and released L5-S1 total disc prosthesis.
See page 165 for colour figure.

In general, the removal leaves a big defect with a height of 2.5 to 4 cm (Figure 2.4). After vigilant clearing of periprosthetic fibrous tissue and sclerotic bone, the defect is filled with an autologous/homologous solid and/or cancellous bone grafting and/or tricalcium phosphate. We now favor an allograft strutgraft. After ensuring that there are no vascular lesions to be addressed, the retraction system is removed. The wound is closed in layers in the standard manner.

Figure 2.4 Defect after removal of the artificial disc. See page 165 for colour figure.

RESULTS AND COMPLICATIONS

The average operation time for the TDR retrieval was 152 minutes (range: 85 to 250 min). In this retrieval study group, we had 2 left common iliac artery and 2 left common iliac vein lesions, 1 bleeding from the ascending lumbar vein and 1 pronounced bleeding from the intervertebral defect. All the vascular lesions could be addressed immediately by the vascular surgeon and did not result in extensive blood loss. Major blood loss (total 5100 ml) was only encountered in 1 case during the release of an endplate by chiseling, possibly from the epidural plexus and the vertebral bone itself. This bleeding was eventually stopped, by pressing in cancellous bone graft in the bleeding defect. The average blood loss in the other cases was 351 ml (range: 60 to 1000 ml).

One patient, who had a common iliac vein bleeding per-operatively that was sutured, developed postoperatively a severe deep venous thrombosis of the left leg, despite prophylactic anticoagulation with low molecular weight heparins.

In the 1 case where we had to go transperitoneal, we encountered a small colon lesion that was easily closed. Another patient acquired a small lesion of the left ureter and subsequent necrosis of the ureter, caused by an aberrant position, directly in front of the L4-5 prosthesis and by difficult retroperitoneal dissection owing to scar tissue. This resulted, eventually, in resection of the left kidney.

Two patients had severe left leg pain and hypesthesia in the groin/thigh region probably owing to neuropraxia of the genitofemoral or ilioinguinal nerve. This might be a result of the psoas muscle retraction. No motor lesions occurred.

Other complications that can occur but were not encountered in our series are wound infection and injury to the (superior) hypogastric plexus, which may induce erectile dysfunction and retrograde ejaculation.¹²

The clinical results of this series of patients were described in a separate article.¹³

Additional Surgery

All patients had an instrumented posterior fusion as additional surgery for the removal of the disc prosthesis. The additional posterior fusion took place about 1 to 2 weeks before or after removal of the prosthesis in 9 patients. In 10 cases, the posterior fusion was performed as a second operation on the same day (as now-a-days is the standard procedure in our practice). In 6 cases, the posterior fusion was performed as a primary operation to address the pain complaints, but this proved to be insufficient; TDR removal was performed a few years later.

The levels addressed for posterior fusion or stabilization extended the level of the removal with anterior fusion in 17 cases owing to adjacent degeneration. In 2 of these patients, the Dynesys flexible fixation was used to address the adjacent degeneration problem. However, the Dynesys instrumentation was removed in both patients because of screw loosening. The other 8 cases had only the index level(s) fused posteriorly.

DISCUSSION

In agreement with Hedman et al.¹⁴, an intervertebral disc prosthesis with articulating properties should have the following features: long endurance preferably lasting for the rest of the life of the recipient, so that the materials of which the prosthesis is composed of are of critical importance to prevent premature disintegration; the prosthesis should generate a normal or near-normal movement compared with the pattern of the healthy spinal motion segment, so that the corresponding facet joints and adjacent level(s) are not overloaded; and long-term fixation is necessary to prevent migration or subsidence.

It seems almost impossible to manufacture a disc prosthesis that possesses all these characteristics. Consequently, many designs have been proposed with frequent "improvements".¹⁵

The polyethylene core of the Charité prosthesis is susceptible to wear and cracks with breakage of the metal wire marker whether or not related to impingement.¹⁶ This polyethylene wear leads to third-body debris in the intervertebral space near the spinal canal, which might result in vertebral osteolysis.^{4,17} We saw polyethylene wear

to a minor or major degree in most prostheses we removed, and an inflammatory periprosthetic reaction. Good sizing and good placement seems to be difficult. As in our series, as in the series of revisions of McAfee et al.³, most retrieved prostheses were originally not placed in the ideal position or undersized.² But, in some cases (in our series, 4 of 29), there was no radiologic sign of malpositioning or malsizing, indicating that perfectly implanted disc prostheses may also fail.

The main reason for TDR removal is persistent or recurrent severe back pain with or without leg pain. Another reason may be migration or luxation of the TDR with possible damage to the great vessels. In case of persisting severe back problems, we started in 15 patients with a posterior fusion without removal of the TDR. But, as our own experience taught us that a successful posterior fusion alone in most cases resulted in unsatisfactory results, we combine the posterior fusion with TDR removal in all cases if the patient accepts the inherited risks of the retrieval surgery.

We use an anterolateral approach to retrieve the L4-L5 (and higher) prosthesis to leave the great vessels lying anterior to the spine in place, as they are more fragile and it is risky to manipulate them because of scarring from previous surgery. Despite the potential dangers for removal surgery, removal of the Charité artificial disc was feasible, except for 1 case. We had, except for 1 case (5100 ml), minor average blood loss because of the immediate availability of a vascular surgeon, proving his value in this kind of surgery.

We conclude that retrieval surgery of Charité TDRs is feasible and relatively safe, but has its inherited risks because of nearby vascular structures and scar tissue. We suspect that the removal of keeled TDRs, such as the Prodisc and Maverick implants, is more difficult, and more bone removal is needed when above L5-S1, a lateral approach is chosen to avoid mobilizing the great vessels for a second time.

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CHAPTER 3

Complications and reoperations of the SB Charité lumbar disc prosthesis: experience in 75 patients

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ABSTRACT

Artificial disc prosthesis show fair to good short- and mid-term results. Long-term results are becoming apparent now, however, the incidence of late complications with this procedure remain poorly understood. In this report we will analyse late complications and discuss our experiences with salvage operations in patients with persistent pain after SB Charité disc prosthesis implantation.

Seventy-five patients with persistent leg and back pain after insertion of an artificial disc prosthesis were enrolled in the study. In this negative selection frequently occurring late-complications were subsidence, wear, adjacent disc degeneration, facet joint degeneration and migration.

In 15 patients we performed a posterior fusion without disc removal, and in 22 patients we removed 26 prostheses and performed a posterior and anterior fusion. The visual analogue scale (VAS) and Oswestry were examined before the salvage operation and after a follow-up period of at least 1 year, which is not yet available in all patients. The VAS and Oswestry decreased in the posterior group (n=10) respectively from 8.0 (SD 0.9) to 6.3 (SD 2.1) and from 57.0 (SD 17.0) to 44.6 (SD 20.4); and in the disc removal group (n=14) respectively from 8.0 (SD 0.9) to 5.6 (SD 2.7) and from 56.3 (SD 14.0) to 43.0 (SD 20.7).

Serious late complications may occur following total disc replacement. Removal of the SB Charité artificial disc is feasible but with inherent risks. Removal of the disc prosthesis gives slightly better results than posterior fusion alone after a follow-up of at least 1 year.

INTRODUCTION

Degenerative disc disease (DDD) is a major cause of pain and disability, with great social and financial impact, playing an increasing role in modern society.¹ Several surgical techniques have been developed to treat DDD. Spinal fusion is seen as the “gold standard”, but nowadays artificial disc prostheses are an alternative method.² The artificial disc should preserve motion, stability and normal function of a spinal segment. Also, less adjacent segment degeneration is expected.²⁻⁵ In theory, this procedure has many advantages over spinal fusion. A spinal fusion does eliminate motion and can cause overloading and early degeneration of the adjacent levels, although usually appearing only after 10–15 years.⁶⁻⁹

Results after implantation of the SB Charité artificial disc prosthesis are diverse. Short- and mid-term results are fair to good.^{2,10-12} The FDA-IDE study, in which the SB Charité artificial disc was tested for approval in the US, showed a FDA-defined, overall clinical success rate of 57.1% after 2-year follow-up.^{5,13} For the IDE study, the procedure was only judged to be successful if four criteria were satisfied: (1) greater than 25% improvement in Oswestry disability index; (2) no device failure; (3) no major complications; and (4) no neurological deterioration compared to preoperative status. Consequently, the composite definition of success employed in the IDE study makes it difficult to compare with other studies that employed different success criteria.

In a 10-year follow-up period, Lemaire et al.² found that 90% of patients had good to excellent clinical outcome. On the other hand, in the only available long-term study of Putzier et al.¹⁴ with an average follow-up of 17 years, the investigators found no evidence that long-term results of the disc prosthesis were superior to spinal fusion.¹⁴ It remains unclear whether the early fair to good results obtained with an artificial disc will be consistently maintained with a longer follow-up period.¹⁴⁻¹⁷

In the Netherlands, more than 1000 patients have been implanted with a SB III Charité (Link, Germany) disc prosthesis starting in 1989. As these patients received the implant during routine clinical practice, they were not the subjects of a randomized trial. However, 50 patients (75 arthroplasties) were enrolled in a prospective observational trial, and at 2 years the clinical success rate was found to be 70%.¹²

Since 1989, there have been many changes in the available implant sizes, surgical instrumentation, and patient indications. Although the basic “SB III” design has remained the same throughout the past 18 years, there have also been evolutionary changes in the polyethylene (PE) resin, sterilization, and endplate fixation technology. Starting in 2004, the SB III design has been renamed the Charité artificial disc and is currently produced by a different manufacturer (DePuy Spine, Raynham, MA, USA). Despite these aforementioned changes, it remains crucially important to fully understand the long-term clinical failure modes of early total disc replacements, as they form the foundation for judging the performance of contemporary implant designs and treatment paradigms.

At present, we have treated 75 patients at our clinic with persistent leg and back pain after insertion of the SB Charité disc prosthesis. The incidence of complications following Charité artificial disc implantation at our institution has proven difficult to deduce because all operations were performed elsewhere. At 2 years of follow up, investigators from the hospital implanting the disc prosthesis reported that 17 out of 50 (34%) patients required secondary surgery, and there were three (6%) reported serious complications.¹² The purpose of this study is to analyse late-complications after insertion of a disc prosthesis, and to describe our experiences with salvage operations in this difficult patient group.

MATERIALS AND METHODS

Patients

Approximately more than 1000 Dutch patients, suffering from serious and constant back and leg pain, have been implanted with a SB III Charité (Link, Germany) artificial disc prosthesis in the lower lumbar spine.

Over the last 10 years, 75 patients of this cohort, with persisting back and leg pain and being unsatisfied with their clinical situation, were seen at the orthopaedic outpatient clinic of the University Hospital of Maastricht (UHM). They were seen by a different orthopaedic surgeon (AvO and LvR) than the surgeon who performed the prosthesis implantation. Twenty-seven of these cases have already been reported previously.¹⁷

Forty-one patients were female with an average age at the time of disc implant of 42 years and 7 months (30–63 years) and 34 patients were male with an average age of 40 years and 9 months (30–51 years) at the time of disc implant (Table 3.1). The operated levels and the year the patients received their artificial disc implantation is shown in Table 3.1.

Forty-six out of these 75 patients needed one or more salvage operations after their artificial disc implant. Indicators for reoperations were primary absence of pain relief, new pathology according to radiography, CT-scan or MRI in adjacent segment(s), subsidence, facet joint arthrosis or migration of the prosthesis. In our hospital, we performed posterior fusion in 15 patients without disc removal, and in 22 patients we removed 26 prostheses and performed an anterior and posterior fusion. In addition, seven patients received posterior fusion elsewhere, and in two patients the disc prosthesis was removed elsewhere (Figure 3.1).

Table 3.1 Patient characteristics

Sex	N	Age at artificial disc insertion
Males	34	40 years and 9 months (30-51)
Females	41	42 years and 7 months (30-63)
Operated Level		
<i>First level</i>		
L2-L3	1	
L3-L4	3	
L4-L5	22	
L5-S1	30	
<i>Second levels</i>		
L3-L4, L5-S1	1	
L4-L5, L5-S1	16	
<i>Third levels</i>		
L3-L4, L4-L5, L5-S1	1	
L2-L3, L4-L5, L5-S1	1	
Time Disc Implantation		
1989-1994	25	
1995-1999	30	
2000-2005	20

Figure 3.1 Overview of reoperations after disc prosthesis implantation (UHM: University Hospital Maastricht)

Surgical method of disc prosthesis removal

The disc prosthesis was removed by a team consisting of a vascular surgeon and an orthopaedic surgeon. The patient was placed under general anaesthesia and positioned in supine position (for level L5–S1) or in a semilateral position (for level L4–L5 or higher).

A disc prosthesis at level L4–L5 was removed via anterolateral lumbotomy, without mobilisation of the great vessels. A disc prosthesis at level L5–S1 was removed through the original left retroperitoneal approach or alternatively via right retroperitoneal, between the great vessels. To remove the disc prosthesis one of the endplates was released by undercutting and removal of some bone after cleaning of fibrous tissue. The metal endplate was gripped and removed with twisting and pulling manoeuvres. Then the core and second endplate was easily released and removed.

The gap between the vertebral bodies after retrieval of the disc prosthesis was mostly 2.5–3 cm high. This was filled with an autologous strut graft in 2 patients, artificial bone in 3 patients and allograft strut grafts and allograft bone chips from femoral heads in 17 patients. We now favour the insertion of allograft strut grafts from the bone bank.

Clinical performance and complications

Before the orthopaedic surgeons in our outpatients clinic performed reoperation, they evaluated the images of X-ray, CT-scans, MRI and if necessary discography on the presence of late complications.

Clinical examination included the ten-point visual analogue scale (VAS), ranging from 0 points for “no pain” and 10 points for “severe pain”, and the Oswestry low back pain disability questionnaire. The VAS and Oswestry were examined before the salvage operation and after a follow-up period of at least 1 year after this operation. The 1 year follow-up VAS and Oswestry are not yet available in all patients.

Statistical analysis

Analyses were performed using SPSS, release 12.0.1. Nonparametric tests, i.e. Mann–Whitney and Wilcoxon, were used to test mean. Significance was indicated by *P* values less than 0.05.

RESULTS

Late complications

An overview of late complications after disc implantation is shown in Table 3.2. They included the following: 39 patients showed subsidence of the disc prosthesis, in 24 of

these patients the disc prosthesis was considered too small. Thirty-six patients showed signs of adjacent disc degeneration, narrowing of the disc and osteophytes on conventional X-rays. In 17 patients this was not obvious before artificial disc insertion on plain X-rays and discography. Eleven patients with multi-level adjacent disc degeneration had developed degenerative lumbar scoliosis. In 25 patients facet joint degeneration was seen on CT-scans. In six patients the disc prosthesis showed anterior migration and in two patients posterior migration of the disc prosthesis occurred. In ten patients we discovered breakage of the metal wire around the core (Figure 3.2).

Less often the surgeons noticed the subsequent late complications. In one case severe osteolysis was seen in the sacrum in a ruptured and severely worn L5–S1 case. In another case a subluxation of the PE core and an adjacent osteoporotic compression fracture was noticed. In five patients radiological wear of the disc prosthesis was obvious due to loss of height of the core, or sclerosis and cysts around the prosthesis on CT-scan.

Table 3.2 Overview of late complications after receiving a disc prosthesis (patients can have more than one complication).

Late complications	Number of patients
Subsidence	39
Disc prosthesis too small	24
Adjacent disc degeneration	36
Degenerative scoliosis	11
Facet joint degeneration on CT scan	25
Anterior migration	6
Posterior migration	2
Breakage metal wire	10
Wear	5
Severe osteolysis	1
Subluxation PE core	1

Figure 3.2 Example of removed polyethylene core L4-L5 (left) and L5-S1 (right) (6,5 years after insertion) with a fracture of the metal wire and damage of disc prosthesis. See page 166 for colour figure.

Study population

The group of 15 patients receiving posterior fusions in our hospital without removing the prosthesis, consisted of 8 men and 7 women. Mean age at their revision surgery was 49 years and 9 months (34–76 years) and mean time-interval between their disc implant and revision surgery was 7 years and 11 months (2–15 years).

Facet joint degeneration was noticed during all operations. Afterwards, we removed the disc prosthesis in four patients of this group because of persisting pain. Nowadays, we advise disc prosthesis removal in conjunction with fusion surgery, assuming that the disc prosthesis can remain a pain source even after solid posterior fusion.

So far, we retrieved 26 prostheses in 22 patients (17 females, 5 males). The additional posterior fusion took place in nine patients 2 weeks before or 2 weeks after the removal of the disc prosthesis. In the other 13 patients, posterior fusion was done as a second operation on the same day as the removal. Nowadays this is the standard procedure in our hospital. The mean interval between insertion and retrieval of the disc prosthesis was 8 years and 11 months (3–16 years). The mean age at retrieval of the disc prosthesis was 50 years (40–72 years).

A pre- and post-operative radiograph of one case, in which we removed the disc prosthesis L4–L5 and L5–S1 and performed a posterior and anterior fusion, is shown in Figures 3.3 and 3.4.

Figure 3.3 (A) Anteroposterior and (B) lateral radiograph of the lumbar spine 3 years and 9 months after disc replacement at L4-L5 and L5-S1.

Figure 3.4 (A) Anteroposterior and (B) lateral radiograph of the lumbar spine 9 months after revision surgery.

Intraoperatively we twice encountered a lesion of the left common iliac vein (in L5–S1 cases), once a lesion of the left common iliac artery (in an L4–L5 case) and once a small incomplete colon lesion. These complications could all be controlled by the vascular surgeon with relatively little blood loss. Mean blood loss for the anterior procedure was 753 cc (60–5100 cc). In one patient profound bleeding was encountered from the vertebral body bone and possibly the epidural plexus underneath the distal endplate of an L5–S1 disc prosthesis. This was controlled by packing with bone bank chips and gel foam, however the total blood loss in this two-level case was 5100 cc.

In another patient we planned to remove the disc prosthesis, however, due to a rupture of the small intestine during the access phase, we decided only to perform a posterior fusion.

Preliminary clinical results

General clinical information for both revision strategies, with a follow-up period of at least 1 year, is shown in Table 3.3.

Table 3.3 Clinical information for both revision strategies (with a follow-up period of at least 1 year).

Nr	Sex	Year Index surgery	Age index surgery	Levels	Year re-operation	Removal/ Fusion	Extra procedures	% improvement VAS	% improvement Oswestry	Clinically improved Oswestry (>25%)
1	f	1993	44	L2-L3	2003	Fusion	None	41.18	27.50	Yes
2	m	1995	41	L4-L5	1997	Fusion	None	-33.33	-44.44	No
3	f	1992	63	L5-S1	2005	Fusion	None	-14.29	-24.34	No
4	m	1997	30	L5-S1	2001	Fusion	None	27.78	16.67	No
5	f	2000	42	L4-L5	2003	Fusion	None	12.50	14.71	No
6	f	1996	42	L4-L5, L5-S1	2003	Fusion	None	27.78	6.45	No
7	f	2002	38	L4-L5, L5-S1	2003	Fusion	None	29.41	16.13	No
8	m	1997	48	L5-S1	2004	Fusion	None	86.67	82.76	Yes
9	m	1995	37	L5-S1	2005	Fusion	None	18.75	0.00	No
10	f	1997	34	L5-S1	2002	Fusion	None	0.00	74.07	Yes
11	m	1992	37	L4-L5	2005	Removal	None	29.41	missing	missing
12	f	1995	33	L4-L5	2006	Removal	None	-12.50	25.00	Yes
13	m	1989	44	L4-L5	2005	Removal	None	-12.50	5.41	No
14	f	1991	39	L4-L5	2002	Removal	None	12.50	30.00	Yes
15	f	1995	39	L5-S1	2004	Removal	None	87.50	56.25	Yes
16	f	1999	46	L4-L5, L5-S1	2005	Removal	None	76.47	73.08	Yes
17	f	1992	33	L3-L4, L5-S1	2005	Removal	None	62.50	62.50	Yes
18	m	1998	46	L4-L5	2004	Removal	None	11.11	12.50	No
19	f	1992	32	L2-L3, L4-L5, L5-S1	2004	Removal	None	9.09	38.10	Yes
20	m	2001	47	L4-L5	2005	Removal	None	55.56	16.80	No
21	m	1995	39	L4-L5	2005	Removal	None	-6.67	0.00	No
22	f	2002	37	L4-L5, L5-S1	2005	Removal	Dynesys	62.50	3.33	No
23	f	1990	55	L4-L5	2006	Removal	None	11.11	10.00	No
								14.29	13.97	No

Ten patients receiving posterior fusion without removal of the prosthesis, have at this moment a follow-up period of more than 1 year since their posterior fusion. The mean VAS before posterior fusion was 8.0 (SD 0.9) and after posterior fusion 6.3 (SD 2.1) (Figure 3.5).

Figure 3.5 VAS scores before and after salvage operation.

Furthermore, 14 patients had a follow-up period of more than 1 year since their disc prosthesis removal. Two disc removal patients had insertion of the Dynesys fixation system (one patient had a follow-up of at least 1 year), in addition to the fused disc prosthesis level, for multiple adjacent levels degeneration. This multilevel Dynesys instrumentation was recently removed in both patients due to screw loosening. The VAS score in this group decreased significantly from 8.0 (SD 0.9) before disc prosthesis removal to 5.6 (SD 2.7) after removal ($P < 0.05$) (Figure 3.5). The percentage of improvement after revision surgery in both groups is shown in Figure 3.6.

The mean Oswestry decreased in the posterior fusion group (n=10) from 57.0 (SD 17.0) to 44.6 (SD 20.4), and in the disc removal group (n=13) from 56.3 (SD 14.0) to 43.0 (SD 20.7) (Figure 3.7). This questionnaire is missing in one patient from the disc removal group. According to the abovementioned IDE-criteria, in which an improvement of $\geq 25\%$ was considered to be clinically improved, 3 out of 10 patients in the fusion group and 6 out of 13 patients in the disc removal group were clinically improved (Table 3.3; Figure 3.8).

Figure 3.6 Percentage change in VAS scores in both revision strategies.

Figure 3.7 Oswestry scores before and after salvage operation.

Figure 3.8 Percentage change in Oswestry scores in both revision strategies.

Postoperative complications

Two patients from the posterior fusion group developed pseudo-arthritis postoperatively.

We encountered five postoperative complications in the disc removal group. One patient developed deep venous thrombosis (DVT) of the left leg after suturing a left common iliac vein lesion. In two patients, decreased sensitivity in the left groin and upper leg was noticed, which was partially reversible. Two patients have severe pain and decreased diffuse strength in the left leg postoperatively. In one of these patients these complaints are diminishing at the moment. Presumably, excessive retraction of the lumbosacral nerves in the psoas muscle played a role in these left leg complications.

DISCUSSION

Seventy-five patients with persistent leg and back pain after insertion of a SB Charité disc prosthesis were studied. The causes of persisting pain were thought to be related to the following late-complications: subsidence, migration, wear of the disc prosthesis, facet joint degeneration or adjacent degeneration in various combinations. Good placement and good sizing of the disc prosthesis appeared problematic for many of the patients in our series. In 39 patients we saw subsidence of the disc prosthesis, and in our judgement X-rays showed that in 24 of these patients the disc prosthesis was too small. Whether suboptimal sizing and placement resulted from initial surgical technique, or from historical limitations in instrumentation and/or sizing availability remains unclear. Fixation of the disc prosthesis can be inadequate, giving subsidence and migration of the disc prosthesis. Migration can probably be prevented by coating of the metal plate, but subsidence probably not.

Previous studies suggested that adjacent degeneration is prevented after disc replacing surgery.¹⁸⁻²⁰ However, in our study 36 patients showed adjacent disc degeneration. This could be the result of the DDD itself, spreading to multiple levels of the spine, and/or be the consequence of stresses on adjacent levels, generated from the unphysiological motion and functioning of the disc prosthesis.

Concerning the 25 patients in which facet joint degeneration was visible on CT-scans, we hypothesized that an instability is created after removal of the anterior longitudinal ligament and the annulus fibrosis. Replacement with an unconstrained prosthesis will accentuate this instability, especially in extension and axial rotation. The facet joints will be the only restrictor of axial rotation and will degenerate with time.

Because of persisting back and leg pain we performed a posterior fusion without disc removal in 15 patients. Initially, the results were disappointing in most patients, and we therefore started to remove the disc prosthesis. In all patients with removal of the

disc prosthesis, PE wear was observed in minor or major degree with surrounding inflammatory fibrous tissue containing PE wear debris. The association between periprosthetic tissue inflammatory reactions and clinical manifestations of pain is not clear at the present time and will be studied further. It is speculated that with removal of the disc prosthesis and the inflammatory periprosthetic tissue, the patient may obtain better pain relief than after only posterior fusion.²¹ This hypothesis obviously needs further support with a larger number of more carefully selected patients.

Clinical results after disc prosthesis revision performed in our hospital were diverse. Patients with short segment fusions seemed to fare better than patients with long segment fusions or long flexible fixations with the Dynesys system. At present, the small number of patients and the large number of potential factors influencing the outcomes (Table 3.3), precluded assessment of a significant association between revision strategy and outcome in the current study.

The mean VAS for pain after disc prosthesis removal was reduced significantly with 2.4 points, from 8.0 to 5.6, whereas the VAS in patients with posterior fusion showed a smaller decrease from 8.0 to 6.3. However, the analyses are based on a small number of cases and a greater number of patients with longer follow up are necessary for a more definitive conclusion.

In a collaborative study by Kurtz et al.²² it was concluded that artificial discs exhibited wear mechanisms similar to artificial hips and knees. Since the operated patients are mostly between 30 and 50 years at the time of their disc implantation and these young patients will be likely very active, wear may become a clinically significant issue at long term follow-up. The clinical relevance of wear in total disc replacements is the subject of intense, ongoing research at our institutions.

A major point to consider is that, in contrast with a posterior fusion, retrieval of an artificial disc prosthesis can be dangerous because of nearby vascular structures and scar tissue from the original surgery. However, in our hands, disc removal surgery proved feasible in all but one case in this patient group (26/27 disc retrievals, 96%). Due to the availability of a vascular surgeon during the retrieval surgery average blood loss could be restricted.

In conclusion, serious complications may arise following total disc replacement surgery, however, as yet relatively few data are available to provide the basis for treatment of patients with clinically failed artificial discs. Removal of the disc prosthesis with anterior and posterior fusion gives slightly better results than posterior fusion alone after a follow-up of at least 1 year. Removal of the SB Charité artificial disc was feasible but with inherent risks. As more data become available, perhaps revision artificial disc surgery may become a more common operation for spine surgeons in the near future.

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CHAPTER 4

Clinical outcomes of two revision strategies for failed total disc replacements

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Submitted

ABSTRACT

Purpose

To compare mid-term clinical outcomes of two revision strategies for patients with failed SB Charité III total disc replacements (TDRs).

Methods

Eighteen patients with a failed TDR underwent posterolateral instrumented fusion (*fusion group*); and in 21 patients the TDR was removed and the intervertebral defect was filled with a bone strut graft, followed by an instrumented posterolateral fusion (*removal 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

Mean follow-up was 3.7 year (range 1.0-6.4) in the removal group and 4.4 year (range 0.7-11.0) in the fusion group. Although the removal group showed a significantly lower VAS and ODI score post-revision surgery as compared to preoperatively ($P<0.01$, $P=0.01$ respectively), no significant differences were found between the removal and fusion groups before and after revision surgery in VAS and ODI. A clinical relevant improvement in VAS and ODI was found in 47% and 21% respectively in the removal group, and in 22% and 27% respectively in the fusion group. Substantial complications were observed only in the removal group.

Conclusions

Both procedures showed improvement clinically. There were no significant additional benefits of removing the TDR as compared to fusion alone at mid-term follow-up. The clinical decision to remove the TDR should be carefully weighed up against potential risks and complications of this procedure.

INTRODUCTION

Lumbar total disc replacement (TDR) is increasingly used in the surgical treatment of degenerative disc disease (DDD). TDR aims to remove the pain source while preserving vertebral motion at the degenerative operated level(s) in order to prevent the development of adjacent segment degeneration.¹⁻⁶ The debate whether TDR is more effective than lumbar spinal fusion in treating DDD is still going on.^{5,7-12} Recently, a prospective randomized study showed that there are no differences in safety and clinical outcomes after TDR as compared to spinal fusion, at a follow-up period of 5 years.⁸ It was further reported that between 2 and 5 year follow-up, only in the TDR group device failures had been observed.⁸

Potential complications after TDR are recurrent back and leg pain, caused by facet joint degeneration, subsidence, polyethylene wear, migration and adjacent segment degeneration.^{5,7,10,13} This warrants the need for surgical revision strategies.¹⁴ In a recent systematic review of Eerenbeemt et al.¹¹ an overall revision surgery rate ranging from 3.7 to 11.4% was found after TDR. An important question we should ask ourselves is: Will revision surgery be beneficial, and if so, what would be the best revision strategy for failed TDR? In a previous study we reported short-term results of two revision strategies with a follow-up of one year, showing that TDR removal gave better results than posterolateral instrumented fusion alone.¹⁵ Larger groups and longer follow-up were thought to be necessary to support possible advantages of TDR removal surgery.

The purpose of this study was to compare the clinical mid-term results of these two revision strategies for patients with a failed SB Charité III lumbar disc prosthesis. Posterolateral instrumented fusion alone was compared with TDR removal combined with anterior lumbar interbody fusion followed by posterolateral instrumented fusion.

MATERIALS AND METHODS

Patients

Ninety patients with a SB Charité III TDR (Waldemar Link, Germany; DePuy Spine, Raynham, MA) were seen in the outpatient clinic. For all these patients TDR implantation had been performed elsewhere. After evaluation, in 39 patients one or more revision surgeries were performed. Indications for revision surgery were recurrent back and leg pain, and the presence of a TDR-related pathology such as facet joint degeneration, subsidence, migration and adjacent level degeneration as observed on plain radiographs, CT-scan and/or MRI.

In 21 patients the TDR was removed and after clearing of periprosthetic fibrous tissue and sclerotic bone, the intervertebral defect was filled with a bone strut graft. In addition, an instrumented posterolateral fusion was performed (*removal group*).¹⁶ In

the 18 other patients posterolateral instrumented fusion without removal was performed (*fusion group*). Because of persisting pain, in eight of these 18 patients TDR removal was performed several years later as a second stage revision surgery (range 1.5–7.5 years). For these eight patients, data were available before and after fusion (stage 1) as well as before and after removal of the TDR (stage 2). An overview of the included patients is shown in Figure 4.1.

Figure 4.1 Overview of the patients who underwent revision surgery after TDR implantation.

*) In these eight patients, pre- as well as post-revision surgery data was available for the fusion and removal revision surgeries.

Clinical outcome measurements and complications

For all patients clinical evaluations were available pre- and post-revision surgery. These evaluations included a 10-point Visual Analogue Scale (VAS) for pain and Oswestry Disability Index (ODI, 0-100 points) questionnaire. According to the FDA-criteria, clinical success was defined as a $\geq 25\%$ improvement in ODI between pre- and post-revision surgery.¹ Similarly, for the VAS pain score, a $\geq 25\%$ improvement was considered as clinically successful. In addition, intra- and post-operative complications of both revision strategies were assessed.

Statistical analysis

Analyses were performed using SPSS 16. Non parametric tests, i.e. Mann-Whitney and Wilcoxon, were used to test means. The mean values were given $\pm$ standard error of the mean (sem); P values < 0.05 were considered statistically significant.

RESULTS

There were no significant differences between the removal group (n=21) and fusion group (n=18) with respect to sex, age at insertion of the TDR, mean time *in situ* of the TDR, and number of operated levels (Table 4.1).

The mean follow-up in the removal group was 3.7 years (range 1.0-6.4 years) and 4.4 years (range 0.7-11.0 years) in the fusion group ($P=0.82$).

Table 4.1 Summary of patient and clinical variables for TDR removal and fusion only group.

	TDR removal (n=21)	Fusion only (n=18)	<i>p</i> -value
Sex ♀: ♂	15:6	10:8	0.31
Mean age insertion TDR	43.4 (range 32-56)	40.7 (range 30-63)	0.11
Mean time <i>in situ</i> TDR	9.1 (range 3.1-16.0)	7.2 (range 1.7-14.8)	0.20
Operated levels:			
1 level	16	14	0.90
2 level	4	4	
3 level	1	0	

VAS pain scores

The mean $\pm$ sem pre-revision surgery VAS score was 7.9 ± 0.3 in the removal group and 7.8 ± 0.2 in the fusion group ($P=0.33$). Post-revision VAS scores were 6.0 ± 0.4 and 7.0 ± 0.4 in the removal group and in the fusion group, respectively ($P=0.09$). In both groups a substantially lower VAS score was observed after revision surgery. Only in the removal group this was a significant decrease at post-revision surgery compared to pre-revision surgery ($P<0.01$) (Figure 4.2a).

The percentage of improvement after revision surgery in both groups is shown in Figure 4.3a. According to the abovementioned FDA-criteria, in which an improvement of $\geq 25\%$ was considered to be clinically successful, 10 out of 21 patients (47.6%) in the removal group and 4 out of 18 patients (22.2%) in the fusion group were clinically improved ($P=0.14$).

Oswestry Disability Index

The mean pre- and post-revision surgery ODI scores were similar between the removal and fusion groups ($P=0.57$, $P=0.61$, respectively). The ODI in the removal group improved from $54.8 (\pm 2.8)$ to $47.9 (\pm 3.8)$ ($P=0.01$), and in the fusion group from $57.3 (\pm 3.9)$ to $48.2 (\pm 4.6)$ ($P=0.06$) (Figure 4.2b).

The percentage of improvement after revision surgery in both groups is shown in Figure 4.3b. A clinically relevant improvement of $\geq 25\%$ was present in 4 out of 21 patients (21.1%) in the removal group and in 5 out of 18 patients (27.8%) in the fusion group were clinically improved ($P=0.69$).

Figure 4.2 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 the standard error of the mean.

Second stage revision surgery

In the fusion group, the 8 patients with persisting symptoms who underwent TDR removal at a later time-point as a second stage revision surgery had a mean follow-up period of 3.1 year (range 0.7-7.3 years) after fusion, while the other 10 patients had a mean follow-up of 5.6 year (range 1.8-11.0 years, $P=0.01$). From the abovementioned 8 patients, a mean follow-up of 3.1 year (range 1.4-5.0 years) was available after their second stage revision surgery, TDR removal.

Figure 4.3 Box plot with A) percentage change in VAS score in both revision strategy group during pre- and post-revision surgery, B) percentage change in ODI score in both revision strategy group during pre- and post-revision surgery. The line represents a clinical success rate of 25%. The error bars represent the upper and lower quartiles.

In the fusion group, there was a significant difference in post-revision surgery VAS score between the patients who underwent TDR removal at a later time-point ($n=8$) and the patients who did not ($n=10$) ($P<0.01$). The patient group who underwent removal as a second stage revision surgery ($n=8$) had a decreased VAS score of 8.1 ± 0.4 to 6.7 ± 0.5 in time ($P=0.06$) (Figure 4.4a).

Patients in the fusion group who would undergo removal as a second stage revision had a similar ODI score as those who would not ($P=0.60$ post-revision surgery stage 1). The patient group who underwent removal as a second revision surgery ($n=8$) had a

ODI score of 52.3 ± 7.3 and 56.8 ± 5.7 after stage 1 and stage 2 revision surgery, respectively (Figure 4.4b).

Figure 4.4 A) Mean VAS scores for the fusion subgroups. B) Mean Oswestry Disability Index scores for the fusion subgroups. Of the 18 patients, eight patients underwent TDR removal as a second revision surgery. The error bars represent the standard error of the mean.

Complications

An overview of the intra- and postoperative complications from both revision procedures is shown in Table 4.2. Intra-operatively, no complications were seen in the fusion group, whereas in the removal group different types of vessel bleeding ($n=6$), a small colon lesion ($n=1$) and decreased sensitivity of the groin ($n=2$) were observed. In one patient 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. In one patient a lesion

of the ureter occurred intra-operatively which necessitated resection of the left kidney at a second stage. In the fusion only group two patients developed a pseudo-arthrosis.

Table 4.2 Intra- and postoperative complications resulting from both revision strategies.

	TDR removal (n=21)	Fusion only (n=18)
Intra-operative	<ul style="list-style-type: none"> - left common iliac artery lesion (n=1) - left common iliac vein lesions (n=2), one resulting in a deep venous thrombosis of the left leg - bleeding ascending lumbar vein (n=1) - pronounced bleeding intervertebral defect (n=1) - major blood loss (5100 cc) (n=1) - small colon lesion (n=1) - decreased sensitivity in the left groin (n=2) 	
Post-operative: 0-3 year	- resection left kidney after ureter lesion (n=1)	- pseudo-arthrosis (n=2)

DISCUSSION

The clinical results of two revision strategies for failed TDR's were studied after a mean follow-up of 3.7 and 4.4 years in the removal and fusion group, respectively. In 18 patients, a posterolateral instrumented fusion without removal was performed and in 21 patients removal of the TDR was combined with anterior interbody fusion followed by posterolateral instrumented fusion. The mid-term VAS and ODI scores significantly improved in the removal group compared to pre-revision surgery, while no significant improvement was found in the fusion group. However, the VAS and ODI scores were comparable for both groups at both time points. A clinical successful improvement ($\geq 25\%$) in VAS was found in 47% in the removal group and in 22% in the fusion group. For ODI, 21% in the removal group and 27% in the fusion group showed a clinical successful improvement. An important point to consider is that, in contrast to the fusion only group with no intra-operative complications, the TDR removal group showed substantial complications in 9 patients (31%) during surgery.

The present study was limited by the relatively small number of cases in both groups which may have induced a type II error. In addition, both surgical groups showed heterogeneous patient characteristics. For example, the number of patients that underwent a second stage revision surgery varies considerably.

In the literature, a wide range of complications has been reported in TDR implantation studies. These complications can be divided into (i) treatment related (e.g. pain, wound problems), (ii) anterior approach related (e.g. vascular injury, retrograde ejaculation), and (iii) prosthesis related (e.g. subsidence, migration).¹¹ The number of reoperations varied between 2.3 and 14%.^{1,6,7,11,12,17} McAfee et al.⁶ reported on 24 patients (9%) who underwent an anterior TDR revision surgery. Those patients who underwent a revision for failed TDR, all had a suboptimal or poor placement of the

TDR. The mean time to revision was 9 months (range: 3 days to 34 months). In four of these 24 patients (16.7%) a vascular injury was encountered.⁶ In another study, from Leary et al.¹⁷, 18 patients underwent an anterior revision procedure after an average follow-up of 6 months (range: 9 days to 4 years). No significant vascular, ureteral and neurological injuries were encountered. However, two patients had a minor left iliac vein injury (11.1%), and one case of retrograde ejaculation was seen that resolved spontaneously.¹⁷ In our patient group we encountered a vascular injury in 6 out of 29 (20.7%). When considering revision surgery it should be realized that removal of the prosthesis has increased risks because of vascular structures and scar tissue. The assistance of a vascular surgeon during TDR removal surgery is strongly recommended.^{16,17} Furthermore, the time between TDR implantation and revision may be of importance. In our patients, TDR removal was performed at much larger follow-up as compared to the previously mentioned studies (mean of 9.4 years, range: 3.1 to 16.3). When TDR removal is indicated, it should be performed as soon as possible after the initial TDR implantation because of the development of scar tissue and adhesions.¹⁷ Complications such as wound infection, injury to the (superior) hypogastric plexus, which may induce erectile dysfunction and retrograde ejaculation were not encountered in our series.¹⁸

In a previous study, we studied periprosthetic fibrous tissues of the first 16 patients with TDR removal using light microscopy.¹³ Results of that study demonstrated the presence of polyethylene wear particles and of periprosthetic inflammatory reactions around a failed TDR in 15 out of 16 patients.¹³ We therefore hypothesized that TDR removal will reduce back and leg pain in failed TDRs because the source of wear debris generation is removed, which may diminish inflammatory mediated pain. The present study showed that, although there was no significant difference between the removal and fusion group during post-revision surgery, the VAS score improved significantly in the removal group after 3.1 years. Removal surgery as a second revision strategy in patients who still experience a high amount of pain after posterolateral fusion reduced VAS pain scores non-significantly.

The aim of the present study was to provide mid-term clinical follow-up data on two TDR revision strategies. In agreement with our previous study¹⁵, the VAS and ODI scores showed similar wide ranges, which indicates substantial variability in outcome between the individual patients. Possible explanations for these wide intervals are patient related factors like number of previous surgeries and number of affected levels. Larger groups will be necessary to assess the effect of patient factors on the success rate of a revision surgery.

In conclusion, the benefit of removing the prosthesis after failed TDR remains unclear. Removal of the TDR may be justified. However, the patient should be counseled about potential risks and complications of this kind of revision surgery which should be carefully weighed up against the possible benefits of TDR removal.

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CHAPTER 5

Undersizing of a total disc replacement and subsidence

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In preparation

ABSTRACT

Background Context

A total disc replacement (TDR) is a surgical treatment of degenerative disc disease which aims to restore and maintain spinal segment motion. A possible complication after TDR implantation is subsidence. Subsidence may be the result of asymmetric implantation, undersizing of the implant or reduced bone quality. The impact of these factors is unknown, nor are objective methods available to quantify subsidence.

Purpose

To develop a method to assess and classify the presence of subsidence of a TDR, and investigate whether undersizing of the implant is related to subsidence.

Study Design

Radiological data analysis study.

Patient Sample

Plain anteroposterior (AP) and lateral radiographs of 42 patients with an L4-L5 SB Charité III TDR (Link, Germany; DePuy, MA) were analyzed.

Outcome Measures

Presence of subsidence of a TDR.

Methods

A custom developed software package implemented in Matlab (Mathworks, MA) was developed to reconstruct the 3D geometry of the bone-implant. A threshold for subsidence was determined by comparing penetrated bone volume and rotation angles between the TDR and bony endplates to that of subsidence as determined clinically. Inter- and intra-observer reproducibility was determined. Finally the quantified subsidence was correlated to the degree of TDR undersizing.

Results

High inter- and intra-observer correlation coefficients were found for quantification of subsidence ($R \geq 0.96$ and $R \geq 0.92$, for L4 and L5, respectively). Subsidence was quantified as a penetrated bone volume $\geq 1300 \text{ mm}^3$ or a penetrated bone volume between $700\text{--}1300 \text{ mm}^3$ in combination with a rotation angle ≥ 7.5 degrees. A reduced risk of subsidence is correlated to $\geq 60\%$ of the area of the bony endplate for L4, and $\geq 62\%$ for L5 being covered by the TDR endplate.

Conclusions

A reliable method to determine subsidence from AP and lateral radiographs was developed. A threshold for the minimum area of the bony endplate that should be covered by the TDR was found to reduce the risk of subsidence. We propose that this approach provide a more objective classification of subsidence and undersizing.

INTRODUCTION

Low back pain caused by degenerative disc disease (DDD) is a major health problem in Western society.¹⁻³ If conservative treatment fails, a surgical intervention may be considered. Besides spinal fusion, total disc replacement (TDR) is increasingly used as a surgical treatment. TDR aims to maintain spinal segment motion with the intention to prevent adjacent level degeneration.⁴⁻⁶ In a recent review, a wide range (10–40%) of complications after TDR implantation has been reported,⁷ among which subsidence of the TDR implant into the bony endplate of the vertebrae appeared to be a relatively frequent complication.⁷⁻⁹

Previously, we reported on a patient group with failed SB Charité III TDR implants (Link, Germany; DePuy, MA),⁹⁻¹¹ of which thirty-nine patients (52%) showed subsidence, presumably caused by a mismatch in size between the TDR and vertebral endplate in 24 patients.⁹ However, De Maat et al.¹⁰ showed that several subsidence cases were not related to undersizing or asymmetric implantation, indicating that ‘perfectly’ implanted TDRs may fail as well.

It is a commonly made assumption that a mismatch in size between a TDR and the vertebra may lead to subsidence. Gstoettner et al.¹² studied the mismatch between vertebral endplates and the size of the TDR implant using CT-scans.^{12,13} Although at level L4-L5 an inappropriate size match (more than 10 mm difference in width between the bony endplate and the TDR endplate) was measured in 97.6% of the vertebral endplates in anteroposterior (AP) direction, and in 78% of the vertebral endplates in mediolateral direction, no evidence was reported that a mismatch actually caused subsidence.¹²

At present, subsidence has not been quantified clinically. Recently, Lee et al.¹⁴ measured the angle between the endplate of a ProDisc-L TDR (Synthes, PA) and the endplate of the vertebra immediately after implantation surgery and during follow-up using lateral radiographs. They concluded that an angular mismatch between the vertebral endplate and TDR implant of less than 5 degrees did not affect the clinical outcome. They did find, however, that subsidence was correlated to an angular mismatch of more than 5 degrees on lateral radiographs at follow-up as compared to immediately postoperative. It should be noted that lateral subsidence, which may be only visible on AP radiographs, could not be detected. In addition, if the TDR had migrated nearly parallel to the vertebral endplate into the vertebra, subsidence was not measured either, while in reality there could have been severe subsidence.

Based on these earlier observations, we hypothesized that subsidence of the SB Charité III TDR could be related to overloading of the bone due to a mismatch in size between TDR implant and vertebrae, causing high stresses on the central cancellous bone of the vertebrae. To test this hypothesis, our study aimed (*i*) to develop a method to assess and classify the presence of subsidence, and (*ii*) to investigate whether undersizing of the TDR is related to subsidence.

MATERIALS AND METHODS

Patient selection

Forty-two consecutive patients with a history of an L4-L5 SB Charité III TDR, who consulted our outpatient clinic with recurrent or persistent low back pain, were included (Table 5.1). The TDRs were implanted elsewhere and had a mean implantation time of 10 years (range 1-19 years). Plain anteroposterior (AP) and lateral radiographs were obtained during routine controls at our outpatient clinic. It was assumed that AP and lateral radiographs were made perpendicular to each other (90 degrees).

Table 5.1 Patients characteristics. Age: age at time of implantation in years. Time in vivo represents time from TDR implantation to last plain radiograph.

	N
Sex (f/m)	19/23
Age (mean, range)	41y, 33-56y
Time in vivo (mean, range)	10y, 1-19y
Number of operated levels	
<i>Single level</i>	26
<i>Two levels</i>	15
<i>Three levels</i>	1

Quantifying subsidence

A custom developed software package implemented in Matlab (Matlab R2009b, the Mathworks Inc., MA) was developed to simultaneously display both AP and lateral radiographs. After selecting the size of the TDR, the TDR is translated and rotated manually by the operator until its outline matches the outline of the TDR in both radiographs (Figure 5.1). Then, the operator identifies the outer left and right points of the bony endplates on the AP radiograph and the outer anterior and posterior points of the bony endplates on the lateral radiograph. These points were connected to create a plane which represent the 3D position of the bony endplates.

Based on these measurements two variables were defined to classify subsidence (Figure 5.2):

1. The volume of bone that has been penetrated by the implants due to subsidence (V_{loss}). This volume was calculated by dividing the bony endplate in infinitive small areas. For each area the average penetration depth of the TDR was calculated and multiplied by this area, leading to the volume of that particular region. In the end, all volumes were summed leading to the total penetrated volume.
2. Rotation angles of TDR implant relative to the bony endplate (α_{AP} and $\alpha_{lateral}$, expressed in degrees (°)).

Thresholds V_{loss} and α beyond which subsidence was to be defined, were determined by an iterative technique.

Figure 5.1 A) Orientation of the metal endplate for L4 shown in a 3D view and B) projections of the orientation on AP and lateral radiographs (red line). All possible configurations of the TDR endplate could be selected. See page 166 for colour figure.

Clinical subsidence

To verify whether the measured subsidence was in agreement with the clinical opinion, the outcome of the software developed method was compared to the physician's impression for the presence of subsidence as estimated by an orthopaedic surgeon (PW). The orthopaedic surgeon scored the presence of subsidence twice to study if there were discrepancies. For further analysis, the first measurement of clinical subsidence was used.

Figure 5.2 (A) Angle between endplate and bony endplate ($\alpha_{lateral}$) on lateral radiograph. The shading on (A) and (B) represents the calculated bone volume loss (V_{loss}). (B) Rotation around the x-axis is measured on AP radiograph (α_{AP}). The bony endplate of the vertebra was defined as the most superior-anterior point till the most superior-posterior point.

Areal Undersizing Index

Using the same software package Matlab, an areal undersizing index (AUI) was defined to quantify differences in area of the bony endplate of the vertebra ($A_{vertebra}$) and that of the metal endplate of the TDR implant (A_{TDR}). The AUI was calculated according to:

$$\text{Areal Undersizing Index} = \frac{A_{vertebra} - A_{TDR}}{A_{vertebra}} \quad (\text{Equation 1})$$

The shape of the vertebral endplate was assumed to be an ellipse fitted through the 4 points defined at the bony endplate earlier. For the TDR endplate a rectangle shape was assumed. When a rotation of the TDR around the longitudinal-axis of more than 15 degrees was measured, this case was excluded due to underestimation of the AUI.

Reliability

To determine the inter-observer reliability of this method, three observers measured all radiographs on both levels (L4 and L5). Two observers (observer 1 and 3) measured twice to determine the intra-observer reliability. For these observers, the mean of both measured AUI was used for further analyses.

Correlation coefficients between the measurements (inter- as well as intra-observer) were calculated.

Statistics

Using SPSS (IBM SPSS Statistics release 19.0.0), independent sample and paired t-tests were used to test means. Inter- and intra-observer correlation coefficients were calculated by Intra Correlation Coefficient (ICC). The association of categorical values was tested by Chi-square test. A significance level of $P < 0.05$ was used.

RESULTS

Clinical subsidence

The two measurements of the orthopaedic surgeon's impression for the presence of subsidence on radiographs differed from each other in 16.7% (7/42) for L4 and in 11.9% (5/42) for L5.

Quantifying subsidence

By combining threshold values for the variables penetrated bone volume and rotation angle of the TDR implant, an objective way to classify subsidence was obtained. Subsidence was assumed to be present if a volume loss of $\geq 1300 \text{ mm}^3$ was measured. Furthermore, subsidence was also assumed if a volume loss between $700\text{--}1300 \text{ mm}^3$ combined with a rotation angle of ≥ 7.5 degrees both AP and/or lateral radiographs was measured.

For the lower endplate of L4 and the upper endplate of L5, in 11 and 17 cases subsidence was classified, respectively. For level L5, one patient was excluded due to projection of fusion instrumentation onto level L4–L5, resulting in an unclear view of vertebra L5. Compared to the classification of clinically relevant subsidence by the orthopaedic surgeon, a sensitivity (Se) of 92% for L4 and 94% for L5 was obtained. For both levels the specificity (Sp) was 84% and 75%, respectively (Table 5.2, Figure 5.3).

Reliability

Eight L4 cases and seven L5 cases had a rotation angle of more than 15 degrees around the longitudinal-axis and were excluded for AUI measurements. The mean AUI of all 34 patients per observer, per level, are given in Table 5.3.

The inter-observer values are shown in Table 5.4. No significant difference between the three observers for both levels was observed. High correlation coefficients between the observers were found for both levels ($R \geq 0.96$, $P < 0.01$).

Table 5.2 Measured subsidence versus clinical subsidence as classified by an orthopaedic surgeon, per level.

		Measured subsidence L4		
		+	-	total
Clinical subsidence L4	+	10	5 (false positive)	15
	-	1 (false negative)	26	27
	total	11	31	42

		Measured subsidence L5		
		+	-	total
Clinical subsidence L5	+	16	6 (false positive)	22
	-	1 (false negative)	18	19
	total	17	24	41

Figure 5.3 Graphical representation of the maximum rotation angle of lateral and AP radiographs versus V_{loss} . The dotted lines represent the threshold values for angle (7.5°) and bone volume loss (V_{loss}) (700 and 1300 mm^3). The asterics represent the patient without clinical subsidence and the squares with subsidence according to the orthopaedic surgeon's impression.

Table 5.3 AUI between bony and metal endplate for vertebra L4 and L5 per observer, given as mean AUI with standard deviation (sd) and range of observations.

Observer	L4	L5
	Mean $\pm$ sd (range)	Mean $\pm$ sd (range)
1	0.34 $\pm$ 0.11 (0.10-0.51)	0.34 $\pm$ 0.11 (0.09-0.56)
2	0.39 $\pm$ 0.13 (0.12-0.57)	0.38 $\pm$ 0.13 (0.10-0.67)
3	0.35 $\pm$ 0.11 (0.11-0.53)	0.35 $\pm$ 0.11 (0.09-0.58)

Table 5.4 Differences between inter-observers for vertebra L4 and L5, including the inter-observer correlation coefficient, given as mean value per observer and *p* value between both observers.

Observer	L4		L5	
	Mean obs	Correlation coefficient <i>r</i> (<i>P</i> value)	Mean obs	Correlation coefficient <i>r</i> (<i>P</i> value)
1 - 2	0.34-0.39	0.97 (<i>P</i> <0.01)	0.34-0.38	0.97 (<i>P</i> <0.01)
2 - 3	0.39-0.35	0.96 (<i>P</i> <0.01)	0.38-0.35	0.98 (<i>P</i> <0.01)
3 - 1	0.35-0.34	0.98 (<i>P</i> <0.01)	0.35-0.34	0.98 (<i>P</i> <0.01)

Intra-observer reliability of L4 did not differ significantly of each other, indicating that both measurements were comparable ($R \geq 0.93$, $P < 0.01$, Table 5.5). For L5 high intra-observer correlation coefficients were found for both levels ($R \geq 0.92$, $P < 0.01$).

Table 5.5 Mean AUI of measurement 1 and 2 for vertebra L4 and L5 per observer (intra-observer), given as mean value per observer and *p* value between both measurements.

Observer	L4		L5	
	Mean1-mean2	Correlation coefficient <i>r</i> (<i>P</i> value)	Mean1-mean2	Correlation coefficient <i>r</i> (<i>P</i> value)
1	0.34-0.35	0.95 (<i>P</i> <0.01)	0.32-0.36	0.92 (<i>P</i> <0.01)
3	0.35-0.35	0.93(<i>P</i> <0.01)	0.35-0.36	0.92 (<i>P</i> <0.01)

Undersizing versus subsidence

Using receiver operating characteristics (ROC) techniques by analyzing the AUI versus measured subsidence a threshold value of 0.40 for AUI on L4 and 0.38 for L5 was obtained with a balance between maximum sensitivity and specificity scores. The computer model obtained for L4 a Se of 86% and Sp of 69% (Chi-square $P=0.02$), and for L5 a Se of 67% and Sp of 62% (Chi-square $P=0.11$) between AUI and measured subsidence of the TDR (Figure 5.4). There was a significant correlation ($P < 0.01$) between the scores the orthopaedic surgeon and the computer model obtained for both L4 and L5.

Subsidence was related to (under)sizing: if more than 60% (1-0.40) of the bony endplate of L4 was covered by the TDR endplate, a reduced risk on subsidence was

observed. For L5, at least 62% (1-0.38) of the bony endplate had to be covered to reduce the risk on subsidence.

Figure 5.4 (A) ROC curve of AUI vs. measured subsidence for vertebra L4, with a sensitivity of 0.86 and specificity of 0.69. (B) ROC curve of AUI vs. measured subsidence for vertebra L5, with a sensitivity of 0.67 and specificity of 0.62. With a ROC curve it is possible to determine a threshold value for AUI to derive the optimal balance between sensitivity and specificity in relationship to subsidence. The striped lines indicate the sensitivity and specificity of the used threshold values.

DISCUSSION

At present, there is no clear evidence to what extent asymmetric implantation, migration or undersizing of a TDR contribute to its subsidence, nor is there a generally acknowledged classification of subsidence. It is known that the clinical opinion of subsidence is subjective and may differ, in this study the presence of subsidence was scored differently by one surgeon on two time points (L4: 16.7% and L5: 11.9%). Therefore, the current study was performed to design a method to measure and classify subsidence, and to determine whether undersizing of the TDR implant is related to subsidence.

A reliable method to measure subsidence of a TDR at level L4-L5 from plain AP and lateral radiographs was developed, with high inter- and intra-observer correlation coefficients ($R \geq 0.92$). Subsidence was quantified by using thresholds for bone volume loss and rotation angles between TDR and bony endplate. Furthermore, subsidence was shown to be related to undersizing of the TDR. A reduced risk of subsidence was

found if more than 60% (L4) or 62% (L5) of the area of the bony endplate of the vertebra was covered by the TDR implant endplate.

Previously, Lee et al.¹⁴ quantified subsidence by measuring the rotation of the ProDisc-L TDR (Synthes Spine, Solothurn, CH) on lateral radiographs. Subsidence was defined as an increase in angle of more than 5 degrees between the TDR endplate and bony endplate on lateral radiographs during follow-up.¹⁴ Furthermore, they measured a mean angular mismatch of 2.3 degrees for L4 one week postoperatively.¹⁴ However, TDRs that migrated parallel into the vertebral endplates were not detected by this method. If in the present study subsidence had been defined as an angular mismatch of ≥ 7.5 degrees for rotation angle, only 5 out of 11 of the level L4 cases (45%) would have been classified as subsidence and 5 out of 17 cases (29%) on level L5. By combining the rotation angle with bone volume loss to measure subsidence, cases where the TDR was migrated parallel into the vertebra were detected as subsidence as well.

Gstoettner et al.¹² defined a distance of 5 mm between TDR implant endplate (Charité and ProDisc-L design) and vertebral endplate on either side as maximum allowed undersizing distance to prevent subsidence (10 mm in total). Using CT data, a mismatch was noted in 97.6% with regard to the anteroposterior diameter. The mediolateral diameter was measured on two locations on CT scans, demonstrating a mismatch in mediolateral diameter in 51.2 and 78% of the endplates.¹² Using their defined 5 mm distance, we found in our series a mismatch of 31% (13 out of 42 cases) for L4 and 20% (8 out of 41 cases) for L5 on lateral radiographs. AP radiographs showed a 90% mismatch both for L4 and L5 (38 out of 42 and 37 out of 41 cases, respectively). These percentages were lower on lateral radiographs and higher on AP radiographs compared to the results of Gstoettner et al.¹², probably caused by differences in the definition of the bony endplate.

The present method to measure subsidence and AUI can easily be implemented in a clinical setting. Two surgeons, without experience with the software package, measured directly after a short instruction. Both surgeons measured independently of each other and derived similar results. The same thresholds for AUI could be used for all observers. From these results it may be concluded that there is no learning curve for this method and only one measurement is enough to derive accurate and reliable data. The introduction of a (semi)automated detection method is not possible because, in most vertebrae, it would be difficult to automate the selection of points due to the presence or absence of multiple areas with high densities (gray values on radiographs), different window settings (difference in gray values between two patients), or over projection on vertebra L5 (AP view only).¹⁵

The method to measure the presence of subsidence is suitable for all lumbar levels up to L5. Unfortunately, L5-S1 could not be measured reliably due to over-projection of L5 onto the sacrum with poor visibility of bony landmarks on plain radiographs. This over-projection will interfere with the selection of predefined points on the radiographs (point could be not visible due to over-projection), resulting in unreliable

values for AUI and the definition of subsidence. In the current study, including patients with an L4-L5 TDR, it was more difficult to identify where the bony endplate of the vertebra exactly starts or ends for level L5. This could be explained due to lordosis of the spine: on AP radiographs, the vertebra L5 was in some cases projected onto the sacrum. Overall, high correlation coefficients were calculated and no significant difference with the other observers was found.

There are some limitations in the current study. First, because patients had been operated elsewhere no direct postoperative radiographs were available. As the direct postoperative position of the TDR was unknown, it was impossible to compare our results with the method of Lee et al. on the SB Charité TDR.¹⁴ More importantly, it was impossible to investigate whether malpositioning or migration of the TDR may have caused subsidence. Secondly, the height of the thresholds for bone volume loss and rotation angle could be biased because the outcome of the clinical score of the orthopaedic surgeon was already known, before thresholds were calculated. Thirdly, we assumed that the radiographs were taken perpendicular to each other. However, as all radiographs were taken during regular patient care according to a standard protocol, it is possible that the angle between both radiographs was larger or smaller than 90 degrees. Large discrepancies, however, could be detected since in that case the fit of the TDR outline would not fit both radiographs at the same time. Small discrepancies could not be detected but will not affect the results substantially. In the present study, in eight L4 and seven L5 patients there was a rotation angle of more than 15 degrees around the longitudinal-axis. Future radiographs should be taken perpendicular according to a protocol. Furthermore, future studies should verify the thresholds in patients with no back or leg pain symptoms, since our method was based on patient with clinical problems after receiving a TDR. Importantly is that the presence of subsidence will have to be related to signs and symptoms for clinical relevance.

In conclusion, a reliable method was developed to measure subsidence and AUI between the vertebral endplate and metal endplate of the TDR implant from plain AP and lateral radiographs. High inter- and intra-observer correlation coefficients were obtained. Our results showed that subsidence appear to be related to undersizing of the TDR in this symptomatic patient group.

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CHAPTER 6

Periprosthetic tissue reactions observed at revision of total intervertebral disc arthroplasty

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ABSTRACT

Wear, wear particle induced inflammation, and osteolysis following total disc arthroplasty were, until recently, not thought to be present due to limited intervertebral motion and the lack of a synovial membrane between the lower lumbar vertebrae. The purpose of this study was to evaluate the periprosthetic tissue reactions associated with total disc arthroplasty revision surgery. Periprosthetic samples of fibrous tissue were collected in all patients during revision surgery of SB Charité III disc prostheses. Revision was indicated for intractable pain after an average of 8 years. Histological evaluation was performed in tissue samples of 16 patients using light microscopy and polarized light microscopy with a magnification of 100×. Polyethylene particles were detected in 15 of 16 patients. The smallest particles were the most numerate. A positive correlation was present between the number of particles per mm² and the extent of the chronic inflammatory reaction in the periprosthetic fibrous tissue. Osteolysis was observed in one patient. In the tissue samples containing polyethylene particles, TNF- α and IL-6 were determined by immunohistochemistry. TNF- α and IL-6 were co-expressed as a subset of mononuclear macrophages and giant cells.

INTRODUCTION

Degeneration of the intervertebral disc is thought to be a major cause of lower back pain. If conservative treatment such as drug therapy, pain management and physiotherapy fails, surgical options can be considered. Artificial disc arthroplasty is an increasingly frequent surgical alternative to spinal fusion, with the aim of preserving the vertebral motion at the operated level(s) and preventing adjacent level degeneration. In the early 1960s, Fernstrom described the first intervertebral disc prosthesis, in which a stainless steel ball was used for nucleus replacement.¹⁻³ Since that time, multiple disc prostheses have been designed for use in the lumbar spine, although the majority of them has never been implanted in humans.^{1,4,5} The SB Charité III disc prosthesis was the first artificial disc that was implanted on a larger scale.^{4,6} For example, more than 1000 patients have been implanted with this prosthesis in the Netherlands. This prosthesis consists of two cobalt–chrome–molybdenum (CoCrMo) endplates, and a sliding ultra-high molecular weight polyethylene (UHMWPE) core.⁷ UHMWPE is also used in prostheses of other joints. The generation of polyethylene (PE) wear debris particles is a well-known phenomenon in total hip and knee arthroplasties.⁸⁻¹¹ These PE wear particles, generated at the articulating surfaces, induce a periprosthetic inflammatory response that can result in osteolysis and may contribute to late aseptic loosening of the implant.¹²⁻¹⁴ Osteolysis has been reported to be associated with the presence of macrophages and pro-inflammatory cytokines such as tumor necrosis factor- α (TNF- α), interleukin-1 (IL-1), interleukin-6 (IL-6) and prostaglandin E₂ (PGE₂).^{12,14} A clinically loose hip or knee prosthesis can lead to pain and instability, necessitating revision surgery.^{13,14}

Until recently it was thought that PE wear was not a clinically relevant topic in total disc arthroplasty (TDA) of the spine.¹⁵ This line of thought was based on the idea that the intervertebral disc is not a synovial joint, and that the motion between the lower lumbar segments is limited.¹⁵ In the literature, only a few case studies concerning PE wear of the disc prosthesis and periprosthetic inflammatory reaction have been reported.¹⁶⁻¹⁸ These studies have shown that PE wear and inflammatory reactions can occur in lumbar disc arthroplasty.

Since the majority of the patients who have received artificial disc arthroplasty was between 30 and 50 years at the time of implantation, and could be expected to have an active life style, wear may become a major issue in these patients at long term follow-up.¹⁹ The wear could limit the durability of the arthroplasty and thus, limit the success of the procedure.

The aim of the present study is to evaluate the periprosthetic tissue reactions in artificial disc arthroplasty obtained at revision surgery. This was achieved using light microscopy and polarized light by scoring the periprosthetic inflammatory tissue reaction, and examining the tissue for the presence and characteristics of PE particles.

MATERIALS AND METHODS

Clinical information of patients

Starting in 1995, 83 patients with persistent back and leg pain after implantation of the SB Charité III disc prosthesis were followed at the Department of Orthopaedic Surgery of the Maastricht University Medical Centre (MUMC). Forty-two of these patients underwent revision surgery at the MUMC. Either posterior fusion without disc removal or disc removal and 360° fusion were performed.

Periprosthetic samples of fibrous tissue were collected from 2004 to 2006 in all retrieval patients. Evaluation was performed on the tissues of the 16 patients in the disc removal group (4 male, 12 female). Revision surgery was performed after an average of 8 years (range 3–16 years). The average age of the patients at the time of the primary operation was 41 years (range 32–56 years). An overview of the clinical information from these 16 patients is summarized in Table 6.1.

Morphometric analysis of PE wear

During revision surgery, periprosthetic fibrous tissue was collected from locations surrounding the prosthesis. Fibrous tissue between the metal endplates and the vertebra was not observed, except in the case with osteolysis. The tissue samples were fixed in 10% phosphate buffered formalin and the bone tissue was subsequently decalcified. During decalcification, the specimens were kept in a 3.5% sodiumformate and 25% formic acid solution²⁰, until they were soft enough for embedding in paraffin. The embedded tissue samples were sectioned in a microtome at a thickness of 4 µm. The sections were stained with hematoxylin and eosin (HE).

In all analyses, a light microscope (Leica DM5000B) was used with a magnification of 100×, with and without polarization filters. Bright-field microscopy was used to examine the histology sections for inflammatory tissue reaction. Polarized light was used to examine histological sections for the presence of PE particles. These particles were identified by their bright white and birefringent spherical appearance.

A stereological software program was employed for histomorphometric analysis (Leica QWin software V3, Cambridge, UK). A maximum of six regions of interest were selected from every HE stained section using a light microscope with polarized light at a magnification of 100×. Only areas where PE particles were visible were selected. Analyzed parameters included mean number of PE particles per mm² of tissue analyzed, length (µm), width (µm), perimeter (µm), roundness of the PE particles and area fraction (%) of the PE particles versus total tissue area.

Table 6.1 Clinical information for all retrieved disc prosthesis.

Patient number	Age at implantation (year)	Gender	Level	Year index surgery	Implantation time (year)	Revision reason(s)	VAS* (pre revision)
1	37	m	L4-5	1992	13	Broken marker wire, subsidence, facet arthrosis.	6
2 [#]	39	f	L5-S1	1995	9	Flattening PE core, broken metal wire, subsidence.	8.5
3	33	f	L4-5	1995	10	Disc degeneration L3-4 above a successful posterior fusion L4-S1.	8
4 [#]	34	f	L5-S1	1997	8	Facet arthrosis L5-S1.	8.5
5	46	f	L4-5	2001	5	Height loss posteriorly at core, facet arthrosis (L4-5, L5-S1), disc degeneration (L3-4).	9.5
6 [#]	46	f	L4-5, L5-S1	1999	6	Both prosthesis had a broken metal wire, subsidence, disc degeneration L3-4.	8
7 [#]	46	f	L3-4	1992	12	Instability/retrolisthesis L1-2, L2-3, pseudoarthrosis L4-5, anterior migration.	9
8 [#]	46	m	L4-5	1998	6	Gross subsidence.	5.5
9 [#]	32	f	L2-3, L4-5	1992	12	Anterior migration L4-5, lateral subluxation, breakage L2-3 disc.	9
10	47	m	L4-5	2001	4	Subsidence, facet arthrosis.	7.5
11 [#]	39	m	L4-5	1995	10	Facet joint degeneration L4-5, degeneration disc L1-2 and L3-4.	8
12 [#]	45	f	L5-S1	1998	6	Broken prosthesis with osteolysis in the sacrum, endplate loosening, facet arthrosis.	9
13	37	f	L4-5, L5-S1	2002	3	Severe facet joint arthrosis L4-5/L5-S1, posterior compression core L4-5.	9
14	34	f	L4-5	1999	5	Lateral subsidence.	9
15 [#]	56	f	L4-5	1990	16	Progressive anterior migration, pressure against aorta, facet arthrosis.	7
16	43	f	L4-5, L5-S1	2002	3	Lateral subsidence L4-5, facet degeneration L5-S1.	9

* VAS = Visual Analogue Scale, ranging from 0 point for no pain and 10 points for severe pain. [#] Tissue sections used for immunohistochemistry (TNF- α and IL-6).

Inflammation

In order to compare the number of PE particles and the level of inflammation, the tissue was graded according to the modified Mirra classification.²¹ This classification was used to identify acute and chronic inflammatory cells, number of giant cells and number of PE particles. The intensity was graded as absent (0), low (1+), moderate (2+) or high (3+). In addition to this classification, we counted the amount of mononuclear macrophages (classified according to the same method as counting lymphocytes). Five microscopic fields of view were scored for each tissue; the averaged results are shown in Table 6.2.

Table 6.2 Classification of histological samples according to the modified Mirra classification.

Patient number	Chronic inflammatory cells (lymphocytes) ¹	Macrophages ²	Giant cells ³	PE fibers < 100 µm in length ⁴	PE fibers 100-500 µm in length ⁵	PE flakes >500 µm in length ⁶
1	1+	2+	2+	3+	1+	1+
2	1+	3+	2+	3+	1+	0
3	0	1+	0	3+	0	0
4	0	2+	1+	3+	1+ *	0
5	0	2+	1+	2+	0	0
6	1+ *	3+	2+	3+	1+ *	0
7	1+	2+	3+	3+	1+	0
8	0	2+	1+	3+	1+ *	0
9	0	3+	3+	3+	1+	1+
10	0	0	0	0	0	0
11	1+ *	3+	0	3+	0	0
12	0	3+	2+	3+	1+ *	0
13	0	2+	0	3+	0	0
14	0	0	0	1+	0	0
15	1+ *	3+	3+	3+	0	0
16	0	2+	0	3+	0	0

¹ 1+: 1-9 cells/high power field (x 500) and/or 1 lymphoid follicle/low power field (x 100), 2+: 10-49 cells/high power field (x 500) and/or 2-3 lymphoid follicles/low power field (x 100), 3+: ≥50 cells/high power field (x 500) and/or ≥4 lymphoid follicles/low power field (x 100); ² 1+: 1-9 macrophages/high power field (x 500), 2+: 10-49 macrophages/high power field (x 500), 3+: ≥50 macrophages/high power field (x 500); ³ 1+: 1-2 cells/medium power field (x 250), 2+: 3-8 cells/medium power field (x 250), 3+: ≥9 cells/medium power field (x 250); ⁴ 1+: 1-9 fibers lying extracellularly and/or 1-9 histiocytes containing ≥ fibers per cell/high power field (x 500), 2+: 10-19 fibers lying extracellularly and/or 10-19 histiocytes containing ≥fibers per cell/high power field (x 500), 3+: ≥20 fibers lying extracellularly and/or ≥20 histiocytes containing ≥fibers per cell/high power field (x 500); ⁵ 1+: 1-3 fibers/low power field (x 45), 2+: 4-9 fibers/low power field (x 45), 3+: ≥10 fibers/low power field (x 45); ⁶ 1+: 1-2/tissue section, 2+: 2-5/tissue section, 3+: ≥6/tissue section; * Histology only found in one microscopic field.

Finally, immunohistochemistry of a subset of tissue sections of 9 of 16 patients (see Table 6.1) was performed according to standard methods.²² Primary antibodies used were mouse monoclonal anti-human TNF- α (HK307, HBT, Uden, The Netherlands), mouse monoclonal anti-human IL-6 (HK308, HBT, Uden, The Netherlands), and mouse monoclonal anti-human CD68 antibody (Dako, Glostrup, Denmark). CD68 was used as a macrophage marker.

Statistical analysis

Analyses were performed using SPSS 15. Relationships between the parameters of the PE particles and inflammation scale were analyzed using Spearman's rho correlation. Significance was indicated by *P* values less than 0.05.

RESULTS

Relationship between number of PE particles and particle size

In the study group of 16 patients, PE particles $>2.05\text{ }\mu\text{m}$ were detected in the samples of 15 patients. These particles were apparent in collagen tissue as well as bone marrow (Figure 6.1a and 6.1b). The particle data were not normally distributed, hence, the median value provided a better description of the central tendency of the data than the mean value. The number of PE particles ranged between 0 and 981 particles/ mm^2 (median: 66 particles/ mm^2). An overview of the number and the structure of the PE particles per patient is shown in Table 6.3.

The PE particles had an oval and mixed morphology, with a median length of $3.92\text{ }\mu\text{m}$ (range: $2.05\text{--}9.04\text{ }\mu\text{m}$) and median width of $1.90\text{ }\mu\text{m}$ (range: $1.16\text{--}2.31\text{ }\mu\text{m}$). The results showed a mean roundness of 1.58 (range: $1.42\text{--}2.05$). The area fraction of the PE particles versus total tissue area showed a broad range from 0.03 to 2.98%. In the patient with the highest area fraction (2.98%) and the highest number of PE particles ($981/\text{mm}^2$) osteolytic changes were seen on a CT-scan.

The particle size frequency distribution included a total of 19,775 particles (Figure 6.2). The smallest particles were the most numerate. In all individual cases the particle size showed a similar exponential distribution. Sixty percent of the particles were less than $5\text{ }\mu\text{m}$ and 90% of the particles were less than $12\text{ }\mu\text{m}$ in size.

A positive correlation ($\rho=0.578$, $P<0.01$) was present between the mean number of particles/ mm^2 and the length of time *in vivo* (years) of the disc prosthesis.

Figure 6.1 Characteristic histological features of the periprosthetic fibrous tissue retrieved from a patient with a Charité disc prosthesis during revision surgery: A) HE stained section observed with light microscopy, B) HE stained section observed with polarized light. Photomicrographs c, d and e were immunohistochemical stained and taken from the area indicated in figure A by the rectangle; C) CD68 (giant cell in the ringed area), D) TNF- α (giant cell in the ringed area), E) IL-6 (giant cell in the ringed area). See page 167 for colour figure.

Figure 6.2 PE particle size frequency distribution.

Relationship between number of PE particles and inflammation

An overview of the semi-quantitative measurements of the tissue according to the modified Mirra classification is shown in Table 6.2. In this study acute inflammatory cells (polymorphonuclear leukocytes) were absent. Of the chronic inflammation cells, lymphocytes were present in a low amount in six of 16 patients. Macrophages, however, were absent in two patients (12.5%), low in one patient (6.3%), moderate in seven patients (43.8%) and high in six patients (37.5%). The amount of multinuclear giant cells was minimal to absent in nine of 16 patients and moderate to high in seven patients.

In one patient no PE particles were found, in most patients (13 of 16 patients) a high degree of small length PE particles was found. In eight patients also some PE particles between 100 and 500 μm in length were visible and in two patients PE flakes larger than 500 μm.

In the tissue containing PE particles and macrophages, the cytokines TNF-α and IL-6 were co-expressed in a subset of CD68 positive giant cells and macrophages (see Figure 6.1c–e).

A positive correlation was present between the number of PE particles per mm² tissue and the number of macrophages ($\rho=0.612$, $P<0.01$), and between the number of PE particles per mm² tissue and giant cells in the periprosthetic tissue ($\rho=0.760$, $P<0.01$).

Also, a positive correlation was present between the length of time *in vivo* (years) of the disc prosthesis and the number of giant cells in the periprosthetic tissue ($\rho=0.674$, $P<0.01$), and between the length of time *in vivo* (years) of the disc prosthesis and the number of PE fibers <100 μm in length ($\rho=0.475$, $P=0.03$).

Table 6.3 Quantitative analysis of retrieved PE wear debris.

Patient number	Mean number of PE particles/mm ²	Number of selected regions	Range length (μm)	Length, mean (μm) (± sd)	Length, median (μm)	Width, mean (μm) (± sd)	Width, median (μm)	Perimeter (μm) (± sd)	Roundness	Area fraction (%)
1	599	6	2.05-943.73	5.82 (±24.20)	3.58	2.15 (±2.18)	2.05	15.72 (±52.18)	1.47	2.53
2	657	6	2.05-165.44	6.13 (±7.46)	4.10	2.05 (±1.13)	2.05	16.25 (±16.59)	1.57	1.22
3	54	4	2.05-24.93	4.30 (±3.48)	3.07	1.78 (±0.85)	1.62	11.96 (±8.22)	1.47	0.08
4	53	6	2.05-167.78	4.75 (±9.67)	3.07	1.63 (±0.86)	1.42	12.66 (±20.63)	1.52	0.07
5	38	3	2.05-33.89	3.79 (±4.82)	2.05	1.18 (±0.56)	1.16	8.96 (±10.90)	1.51	0.04
6	65	6	2.05-125.87	7.13 (±10.27)	4.10	2.07 (±1.10)	2.05	18.26 (±22.09)	1.63	0.15
7	323	6	2.05-135.49	6.13 (±9.05)	3.07	1.88 (±0.96)	1.78	15.88 (±19.50)	1.59	0.42
8	90	2	2.05-162.14	7.51 (±12.66)	3.07	2.25 (±1.34)	2.20	19.23 (±27.59)	1.60	0.80
9	360	6	2.05-1039.8	8.90 (±32.17)	3.70	2.12 (±1.60)	1.78	21.90 (±66.47)	1.65	1.85
10	0	0								
11	50	6	2.05-40.17	4.12 (±3.16)	3.58	1.95 (±0.93)	2.05	11.96 (±7.87)	1.42	0.06
12	981	6	2.05-171.35	7.63 (±8.96)	4.97	2.62 (±1.73)	2.24	20.37 (±20.23)	1.57	2.98
13	67	3	2.05-61.71	6.08 (±8.01)	3.07	1.96 (±1.29)	1.62	15.84 (±18.19)	1.57	0.26
14	2	1	2.31-45.36	15.86 (±15.96)	9.04	3.20 (±1.22)	2.31	37.65 (±34.43)	2.05	0.06
15	299	6	2.05-157.39	7.48 (±9.23)	4.61	2.60 (±2.31)	2.05	20.02 (±21.70)	1.56	0.98
16	17	4	2.05-25.98	5.12 (±4.24)	3.70	2.03 (±1.09)	2.05	14.13 (±9.95)	1.50	0.03

DISCUSSION

Prosthetic wear debris in the lumbar spine, leading to particle disease, was thought to be unlikely because of the absence of a synovium.⁶ The synovium contains macrophages, which could initiate a cellular inflammatory reaction, and thus, the absence of a synovial membrane was hypothesized to prevent the development of particle disease in the intervertebral disc space after implantation.^{5,6,11} However, the results of the current symptomatic patient group, in which the SB Charité lumbar disc prosthesis was removed after an average of 8 years, showed that micron-sized polyethylene (PE) wear debris was present in 15 out of 16 (=94%) patients. The median number of PE particles was 66 particles/mm². These PE particles had a median length of 3.92 µm and width of 1.90 µm. In addition, the results supported the hypothesis that an increased amount of PE particles is associated with an increased chronic inflammatory reaction. An acute inflammatory reaction was not found, however, this is not expected because the lumbar disc prosthesis was already implanted for several years. The cytokines TNF-α and IL-6, with known inflammatory osteolytic activity, were identified in the periprosthetic fibrous tissue in association with activated macrophages, as has been reported with periprosthetic tissues for hip and knee arthroplasties.^{13,23}

As seen in one patient (patient #12), a lumbar disc prosthesis may have the potential to produce PE particles in sufficient quantities, size and shape, to start an osteolytic cascade in the lumbar spine. This was the patient with the highest number of PE particles per mm² tissue and area fraction, 981 particles/mm² and 2.98% respectively. This patient, with osteolytic changes in the sacrum distally from the inferior endplate, was described earlier by van Ooij et al. in more detail.¹⁸ With the exception of this single case, we have seen no other radiologic or intraoperative evidence of osteolysis in any of our 29 revision cases over the past 4 years, nor do any of the unrevised TDA patients we are currently following show radiographic evidence of osteolysis in the lumbar spine. Thus, the overall incidence of osteolysis following TDA continues to be rare. Nevertheless, considering the young age of this patient group and the difficulty of the revision surgery with its potential risks and complications, it is important to realize that clinically significant PE wear debris and osteolysis can occur in the spine.

Previous studies suggested that *in vitro* testing of the lumbar disc prosthesis results in the generation of only small amounts of wear of negligible volume, which would, if valid, ensure the safety of the device.^{15,24} However, these conclusions were based on a functional 10 million cycles wear test under predominantly unidirectional (flexion/extension) motion.^{15,24} Retrieval studies of artificial discs have recently demonstrated that the dome experiences multi-directional motion, similar to total hip replacements.²⁵ UHMWPE components exhibit much greater wear under multi-directional motion as compared with unidirectional motion. Thus, the wear particle

concentrations, when combined with the observations of retrieval analysis, do not support the validity of previously published wear tests for the Charité. This is in accordance with the findings of Serhan et al.²⁴, who mentioned that the *in vivo* wear rates can be significantly different from *in vitro* tests.²⁴

The clinical relevance of PE wear in the lumbar spine continues to be poorly understood, in contrast to PE wear in hip and knee arthroplasties. Many studies have described the periprosthetic tissue reaction including the PE wear rates in both hip and knee arthroplasties.^{8,9,26,27} PE particles are produced in a variety of sizes, and studies using scanning electron microscopy (SEM) have observed that the majority of the PE particles is of submicron size.^{9,28} The produced wear particles can stimulate an inflammatory response, resulting in periprosthetic osteolysis and aseptic loosening of the implant.

Several recent *in vivo* studies reported on the presence of wear debris in the spine, which was similar to the particles observed in hip and knee arthroplasties^{17,18}, whereas other studies did not find signs of wear debris in the lumbar spine.^{29,30} However, David³⁰ reported in his revision case report that no histology was performed because there was no evidence of visible wear debris, lack of local tissue inflammation and osteolysis during revision. The study of Cinotti et al.²⁹ concluded that no wear of the PE core was found, however, this finding was based solely on radiographical evidence. Unfortunately, neither studies performed histology as a scientific basis for their findings.

Another point of interest is that since 1997 the sterilization and packaging process of the polyethylene cores have changed, which has been hypothesized to result in improved wear and strength performance with minimal oxidative degeneration. The earlier PE cores were sterilized in air, while the newer cores are sterilized in an inert environment (i.e. nitrogen). In the present study, in general, the patients with an implant produced after 1997 showed a lower number of PE particles/mm² (158 versus 299 particles/mm²). However, it is difficult to state whether this was a result of the aforementioned changes in fabrication or related to differences in implantation time (5 versus 11 years).

Light microscopy with a magnification of 100× was used in the present study, and the cutoff level to detect PE particles was set at a length of 2.05 µm. This sets the PE particles apart from dust particles. Therefore the light microscope was unable to detect particles of submicron size.^{10,31} Due to the lower limit of detection of 2.05 µm, an overestimation of the mean size and an underestimation of the number of particles are likely. Additional research with electron microscopy is planned in the near future to better determine the size and three dimensional shapes of the PE particles.

CONCLUSIONS

The results of this study demonstrate the presence of wear particles and of periprosthetic inflammatory reactions around symptomatic artificial intervertebral discs. Also, we observed an association between the chronic inflammatory reaction in the periprosthetic fibrous tissue and the presence of wear particles. Unfortunately, with the current study design we were unable to detect the presence of submicron particles that have been shown in literature to be the most bioactive. In this inflammatory tissue the cytokines TNF- α and IL-6 were consistently present. In one patient, we observed osteolysis, which we attributed to the presence of an inflammatory reaction secondary to PE wear particles. It is of clinical concern that wear and inflammatory reactions are possible in the lumbar spine. These findings may limit the longevity of artificial discs, especially since the operation is particularly indicated in younger patients with higher demands.

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CHAPTER 7

Are periprosthetic tissue reactions observed after revision of total disc replacement comparable to the reactions observed after total hip or knee revision surgery?

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ABSTRACT

Study design

Comparative study.

Objective

To compare periprosthetic tissue reactions observed after total disc replacement (TDR), total hip arthroplasty (THA) and total knee arthroplasty (TKA) revision surgery.

Summary of background data

Prosthetic wear debris leading to particle disease, followed by osteolysis, is often observed after THA and TKA. Although the presence of polyethylene (PE) particles and periprosthetic inflammation after TDR has been proven recently, osteolysis is rarely observed. The clinical relevance of PE wear debris in the spine remains poorly understood.

Methods

Number, size and shape of PE particles, as well as quantity and type of inflammatory cells in periprosthetic tissue retrieved during Charité TDR (n=22), THA (n=10) and TKA (n=4) revision surgery were compared. Tissue samples were stained with hematoxylin/eosin and examined by using light microscopy with bright field and polarized light.

Results

After THA, large numbers of PE particles $<6\ \mu\text{m}$ were observed, which were mainly phagocytosed by macrophages. The TKA group had a broad size range with many larger PE particles and more giant cells. In TDR, the size range was similar to that observed in TKA. However, the smallest particles were the most prevalent with 75% of the particles being $<6\ \mu\text{m}$, as seen in revision THA. In TDR, both macrophages and giant cells were present with a higher number of macrophages.

Conclusions

Both small and large PE particles are present after TDR revision surgery compatible with both THA and TKA wear patterns. The similarities between periprosthetic tissue reactions in the different groups may give more insight in the clinical relevance of PE particles and inflammatory cells in the lumbar spine. The current findings may help to improve TDR design as applied from technologies previously developed in THA and TKA with the goal of a longer survival of TDR.

INTRODUCTION

Total disc replacement (TDR) has gained popularity since the early 1990s. In the development of TDR, researchers have used successful biomaterials and design principles that were developed in total hip arthroplasty (THA) and total knee arthroplasty (TKA).¹⁻³ The SB Charité III TDR (Link, Germany) was the first prosthesis that was implanted extensively. This prosthesis is unconstrained and consists of two cobalt-chromium-molybdenum (CoCrMo) endplates and a mobile ultra-high-molecular-weight polyethylene (UHMWPE) core.⁴

Polyethylene (PE) wear is a well known phenomenon in THA and TKA that may ultimately lead to failure of the procedure, due to osteolysis and aseptic loosening.⁵⁻⁷ In this pathogenesis, clinical-, patient-, and implant-related factors are thought to play a role.⁸ PE bearing surfaces generate large numbers of biologically active wear particles which cause periprosthetic inflammatory reactions. Macrophages play an important role in this reaction, because these cells try to eliminate the foreign PE particles in by phagocytosis.^{9,10} Small particles are easily phagocytosed, but cannot be digested. When particles are too large to be phagocytosed by macrophages, multinuclear giant cells are formed.¹⁰ The inability of macrophages and giant cells to degenerate the phagocytosed particles causes increased production of numerous inflammatory mediators and cytokines, such as interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor α (TNF- α) and prostaglandin E₂ (PGE₂).^{7,11}

In THA, the periprosthetic inflammatory response is characterized by macrophages with diffuse cytoplasmatic birefringence, which indicates the presence of small PE particles.^{7,12} These PE particles are generally $<5 \mu\text{m}$.^{7,12} Giant cells and large extra-cellular particles which are commonly found after TKA, have been found in a lesser extent in the interface membranes after THA.⁷ PE particles in TKA have a broader size range, varying from $2\text{-}100 \mu\text{m}$, than those after THA.^{7,12} Osteolysis and aseptic loosening are associated with macrophages containing many small PE particles as most frequently seen after THA.¹² Such small PE particles are generated by adhesion and abrasion, which are the main wear mechanisms in THA. In TKA, subsurface delamination, pitting and fatigue cracking release much larger and differently shaped pieces of PE.¹³⁻¹⁵

Until recently, it was thought that it was unlikely that PE wear would pose a clinically relevant problem in TDR in the lumbar spine. It was hypothesized that there would be little formation of PE wear because of limited motions between the vertebral segments as compared to the hip and knee joint.⁴ Moreover, as the disc space is not a synovial joint, it was assumed that there would not be sufficient particle formation to induce early failure of TDR. However, recent studies documented comprehensive PE wear particles and inflammatory reactions in the periprosthetic tissue collected during TDR revision surgery.¹⁶⁻¹⁹ In a previous study we showed that PE wear particles $\geq 2.05 \mu\text{m}$ are extensively present in periprosthetic lumbar TDR tissue samples in 15 out of 16 symptomatic patients.¹⁸ The periprosthetic inflammatory reaction was

characterized by the presence of mainly macrophages, giant cells and lymphocytes.¹⁸ However, osteolysis in TDR has been rarely reported.¹⁹⁻²² Therefore the clinical relevance of PE wear particles after lumbar TDR remains poorly understood. The purpose of this study was to determine and compare characteristics of PE wear particles and inflammatory reactions in periprosthetic tissue collected during revision surgery of TDR, THA and TKA.

MATERIALS AND METHODS

Patient demographics

Periprosthetic tissue samples were collected during TDR, THA and TKA revision surgery. From 2004 to 2009, in 22 patients a single level SB Charité III disc prosthesis (Link, Germany) was removed. The indications for revision surgery in this patient group were long-term TDR complications, such as pain and migration, subsidence, and/or facet joint degeneration. Retrieval of the TDR was thought necessary to remove one of the possible pain generators. After posterolateral instrumented fusion without TDR removal, the TDR and its surroundings could continue to give rise to pain due to continuous loading. The mean implantation time was 10 years (range: 4.1–16.3 years). The histological findings of these patients were compared with periprosthetic tissue samples of ten THA patients and four TKA patients, collected in 2009 and 2010. The mean implantation time was 13 years (range: 1.9–18.9 years) for the THA patients and 9 years (range: 3.0–21.8 years) for the TKA patients. Patients with a systemic disease, immune suppression or previous revision surgery involving the removal of an implant were excluded from analysis. All had negative intra-operative tissue cultures. An overview of the clinical patient data is shown in Table 7.1. The index surgeries were performed at various clinics.

Histological analyses

Periprosthetic fibrous tissue was collected from the interface membranes surrounding TDR, THA and TKA implants. The retrieved THA and TKA samples were highlighted with black ink to indicate which tissue side had been in contact with the implant. The retrieved tissue samples were fixed in 10% phosphate buffered formalin for 24 hours and bony tissue was decalcified with TBD-1 Rapid Decalcifier (Thermo Shandon, Pittsburgh, USA) for one hour. After decalcification and embedding, the samples were kept in 70% ethanol. Paraffin sections of 4 μm thickness were cut with a microtome (Leica RM2245) and subsequently stained with hematoxylin and eosin (H&E). Light microscopy (Leica DM5000B) was used with bright field and polarized illumination (magnification 100x). Bright field microscopy was used for examining the presence of periprosthetic inflammatory cells, and polarized light to detect PE particles. The cut-off level to detect PE particles was set at a length of 2.05 μm to distinguish between PE and dust particles.

Table 7.1 Clinical data of the SB Charité III TDR patients.

Patient number	Age at implantation (years)	Gender	Level	Year at index surgery	Implantation time at revision (years)	Type PE sterilization	Revision reason(s)
TDR-1	37	m	L4-5	1992	13.5	Air	Pain, broken metal wire, subsidence, facet joint degeneration
TDR-2	39	f	L5-S1	1995	9.2	Air	Pain, flattening PE core, broken metal wire, subsidence
TDR-3	33	f	L4-5	1995	10.6	Air	Pain, disc degeneration L3-4 above a successful posterior fusion L4-S1
TDR-4	34	f	L5-S1	1997	8.5	Unknown	Pain, facet joint degeneration L5-S1
TDR-5	46	f	L4-5	2001	5.3	Unknown	Pain, height loss posteriorly at core, facet joint degeneration L4-5, L5-S1, disc degeneration L3-4
TDR-6	46	f	L3-4	1992	12.7	Air	Pain, instability/retrolisthesis L1-2, L2-3, pseudoarthrosis L4-5, anterior migration
TDR-7	32	m	L4-5	1998	6.2	Unknown	Pain, subsidence
TDR-8	39	m	L4-5	2001	4.2	Unknown	Pain, subsidence, facet joint degeneration
TDR-9	45	m	L4-5	1995	10.2	Air	Pain, facet joint degeneration L4-5, degeneration disc L1-2, L3-4
TDR-10	37	f	L5-S1	1998	6.5	Unknown	Pain, broken prosthesis with osteolysis in the sacrum, endplate loosening, facet joint degeneration
TDR-11	34	f	L4-5	1999	4.9	Inert	Pain, subsidence
TDR-12	56	f	L4-5	1990	16.1	Air	Pain, anterior migration, pressure against aorta, facet joint degeneration
TDR-13	44	m	L4-5	1989	16.0	Air	Pain, subsidence, multiple disc and facet joint degeneration
TDR-14	42	f	L4-5	2000	6.2	Unknown	Pain after posterior pedicle screw fixation and fusion L4-L5, L5-S1
TDR-15	42	f	L4-5	1993	13.7	Unknown	Pain, broken marker wire
TDR-16	43	f	L4-5	1996	10.7	Air	Pain
TDR-17	49	f	L3-4	2003	4.1	Unknown	Pain in lower back and both legs, no bony fusion, prosthesis in excessive extension
TDR-18	55	m	L5-S1	1991	16.3	Air	Pain, pseudoarthrosis L5-S1, subsidence
TDR-19	52	f	L5-S1	1993	15.0	Air	Pain back and left leg pain
TDR-20	50	m	L5-S1	2002	6.4	Unknown	Pain, facet joint degeneration L5-S1, lateral migration of the endplate, disc degeneration L3-4
TDR-21	47	f	L4-5	1993	16.0	Air	Pain, degeneration disc L1-3, facet joint degeneration L5-S1, oblique implantation of prosthesis
TDR-22	43	f	L5-S1	2000	8.4	Unknown	Pain, facet joint degeneration L5-S1

Table 7.1 (continuation) Clinical data of the THA and TKA patients.

Patient number	Age at implantation (year)	Gender	Year at index surgery	Implantation time (year)	Type of implant	Cement	Type PE sterilization	Revised component	Revision reason(s)
THA-1	51	f	1990	18.9	Charnley stem Charnley cup	Yes	Air	Cup+Stem	Pain, aseptic loosening, radiolucent lines around the stem and cup, eccentric position due to wear
THA-2	64	f	1990	18.9	Osteonics Omniflex Osteonics PE cup	Yes	Air	Cup	Pain, aseptic loosening, radiolucent lines around the stem, displacement of the head in the cup due to wear
THA-3	39	m	1994	15.0	Osteonics Omnifit Osteonics MC1 cup	Yes, hybrid	Air	Cup	Pain, aseptic loosening, radiolucency around the cup, bone loss of the acetabulum
THA-4	78	f	2004	5.4	Osteonics Omnifit SHP cup	Yes	Inert	Stem	Pain, aseptic loosening, increased activity on scintigraphy around stem
THA-5	66	m	1995	14.3	Osteonics Omnifit Osteonics PE cup	Yes	Air	Cup	Pain, aseptic loosening, radiolucency around the cup, progressive cup migration
THA-6	44	f	1992	17.3	Osteonics Omniflex Dual Radius cup	No	Air	Cup+Stem	Pain, aseptic loosening after trauma, radiolucent lines around the stem, eccentric position due to wear
THA-7	79	f	1998	11.1	Muller straight stem Osteonics PE cup	Yes	Unknown	Cup	Pain, aseptic loosening, radiolucent lines around the cup, broken marker wire, eccentric position due to wear
THA-8	62	f	1994	15.8	Osteonics Omnifit Dual Radius Cup	No	Air	Cup	Pain, eccentric position of the head due to wear
THA-9	49	m	1994	15.4	Osteonics Omnifit Dual Radius Cup	No	Air	Cup	Pain, eccentric position of the head, radiolucent lines around the cup
THA-10	77	f	2008	1.9	Omnifit HA stem SHP cup	Yes, hybrid	Inert	Cup	Pain, aseptic loosening, bone loss acetabulum
TKA-1	65	f	1987	21.8	Kinemax	Yes	Air	Both components	Pain, aseptic loosening of the tibial and femoral component with advanced wear
TKA-2	65	f	2000	8.9	Kinemax Plus CR insert	Yes	Inert	Both components	Persisting anterior knee pain, aseptic loosening of both components, advanced wear of the tibial insert
TKA-3	55	f	2007	3.0	Nexgen Flex Nexgen LPS insert	No	Inert	Both components	Pain, aseptic loosening both components
TKA-4	46	f	2005	4.7	Richard Genesis Insert 11 DD	Yes	Inert	Both components	Persisting anterior knee pain, aseptic loosening both components

All THA and TKA patients showed intra-operatively negative tissue cultures to rule out a concomitant infection.

Morphometric analysis of PE particles

From each H&E stained section a maximum of six regions containing the most PE particles were selected. For the histomorphometric analysis of PE particles a stereological software program was used (Leica Qwin software V3, Cambridge, UK). Analyzed parameters included number of PE particles per mm² of analyzed tissue, length (µm), width (µm), roundness of the PE particles and area fraction (%) of the PE particles versus total tissue area.

Periprosthetic inflammatory response

The tissue samples were examined, according to a modified Mirra classification, for the presence of chronic inflammatory cells (lymphocytes) and giant cells.²³ In addition to this classification, the number of mononuclear macrophages was counted (classified according to the same method as counting lymphocytes). For each tissue sample five microscopic fields were scored.

Statistical analysis

To compare PE wear particles characteristics and inflammatory reactions between TDR, THA and TKA a Mann-Whitney U test and a Kruskal-Wallis test were performed, using SPSS 16.0. Significance was indicated by $P < 0.05$.

RESULTS

Comparison of quantity, size and morphology of PE particles

PE particles ≥ 2.05 µm were detected in the periprosthetic tissue samples of all patients, except one TDR patient (TDR-8), who did not reveal any PE particles. PE particles were mainly observed in macrophages and giant cells in the fibrous collagenous tissue but were also present in bone marrow (Figure 7.1).

The mean number of PE particles/mm² ranged from 0 to 981, 1 to 1002 and 30 to 602 for TDR, THA and TKA, respectively (non significantly different number of PE particles/mm², $P = 0.53$). An overview of the size and morphology of the PE particles per patient is shown in Table 7.2. For all groups, neither age nor gender were correlated with the mean number of PE particles/mm² (TDR: $P = 0.80$, $P = 0.53$; THA: $P = 0.42$, $P = 0.95$; TKA: $P = 0.27$, $P = \text{cannot be computed}$ (all cases are female); respectively).

The particle size frequency distribution of the THA patients showed that the smaller particles were the most numerous (Figure 7.2). Seventy-five percent of the particles were < 6 µm and 94% of the particles were < 12 µm in length. The TDR frequency distribution was comparable to THA, with 75% of the particles < 6 µm and 90% of the

particles $<12\text{ }\mu\text{m}$ in length (Figure 7.2). In the TKA patients 71% of the particles were $<6\text{ }\mu\text{m}$ and 86% of the particles were $<12\text{ }\mu\text{m}$ (Figure 7.2). The TKA distribution peaked at the small particle length but there was another peak for particles $>25\text{ }\mu\text{m}$. All individual cases showed a similar distribution in curve length per TDR, THA and TKA. TDR and THA particles generally had a round to oval shaped morphology. The shape of TKA particles was highly variable with also larger fibrils and flakes. The area fraction (%) of the PE particles versus total tissue area had a size range from 0.03-2.98, 0.00-1.41 and 0.01-0.26 for TDR, THA and TKA, respectively. The single osteolysis case in the TDR group, does not effect the significance of the outcomes.

Figure 7.1 H&E stained sections containing characteristic histological features of the retrieved periprosthetic fibrous tissue from one patient of each study group. A) Section of a TDR patient observed with bright field microscopy, B) Section of a TDR patient observed with polarized light, C) Section of a THA patient observed with bright field microscopy, D) Section of a THA patient observed polarized light, E) Section of a TKA patient observed with bright field microscopy, F) Section of a TKA patient observed with polarized light. For further explanation see text. See page 168 for colour figure.

Table 7.2 Quantitative analysis of retrieved PE wear debris in periprosthetic tissue obtained during TDR, THA and TKA revision surgery.

Patient number	Region tissue	Mean number of PE particles/mm ²	Number of regions containing PE	Length, median (µm)	Length, range (µm)	Width, median (µm)	Roundness, median	Area fraction (%)
TDR-1		599	6	3.58	2.05-943.73	2.05	1.35	2.53
TDR-2		657	6	4.10	2.05-165.44	2.05	1.50	1.22
TDR-3		54	4	3.07	2.05-24.93	1.62	1.35	0.06
TDR-4		53	6	3.07	2.05-167.78	1.42	1.50	0.07
TDR-5		15	3	3.07	2.05-21.29	1.02	1.35	0.00
TDR-6		323	6	3.07	2.05-135.49	1.78	1.50	0.42
TDR-7		90	2	3.07	2.05-162.14	2.20	1.50	0.25
TDR-8		0	0	-	-	-	-	-
TDR-9		50	6	3.58	2.05-40.17	2.05	1.35	0.06
TDR-10		981	6	4.97	2.05-171.35	2.24	1.48	2.98
TDR-11		2	1	9.04	2.31-45.36	2.31	1.54	0.01
TDR-12		299	6	4.61	2.05-157.39	2.05	1.47	0.98
TDR-13		139	6	3.70	2.05-247.25	1.78	1.50	1.07
TDR-14		16	3	2.31	2.05-5.90	1.02	1.35	0.00
TDR-15		683	6	4.10	2.05-116.46	2.05	1.43	1.26
TDR-16		146	6	3.70	2.05-129.06	1.69	1.50	0.28
TDR-17		26	6	4.10	2.05-30.45	1.69	1.51	0.03
TDR-18		344	6	3.07	2.05-45.78	1.42	1.35	0.29
TDR-19		244	6	3.07	2.05-30.54	1.42	1.35	0.17
TDR-20		20	2	4.10	2.05-20.72	2.05	1.37	0.02
TDR-21		111	6	3.07	2.05-45.07	2.31	1.35	0.15
TDR-22		229	6	3.70	2.05-575.07	1.87	1.50	1.13
THA-1	femur	373	6	4.10	2.05-227.46	1.63	1.51	0.03
THA-2	acetabulum	300	6	3.07	2.05-45.38	1.42	1.40	0.27
THA-3	acetabulum	239	6	3.70	2.05-145.48	2.05	1.50	0.50
THA-4	femur	3	5	4.10	2.05-11.05	2.31	1.35	0.00
THA-5	acetabulum	526	6	3.58	2.05-65.37	1.81	1.42	0.04
THA-6	acetabulum	441	6	3.07	2.05-43.67	1.62	1.35	0.31
THA-7	acetabulum	215	6	2.31	2.05-45.71	2.31	1.35	0.26
THA-8	acetabulum	1002	6	2.31	2.05-311.44	2.31	1.20	1.41
THA-9	acetabulum	277	6	3.70	2.05-120.08	2.19	1.47	0.03
THA-10	acetabulum	1	1	2.05	2.05-9.28	1.02	1.35	0.00
TKA-1	unknown	201	6	4.10	2.05-2265.04	2.05	1.56	0.02
TKA-2	tibia	602	6	4.10	2.05-539.40	2.05	1.60	0.05
TKA-3	tibia	40	6	3.22	2.05-214.17	2.05	1.50	0.26
TKA-4	tibia	30	6	2.31	2.05-15.48	1.02	1.35	0.01

Figure 7.2 PE particle size frequency distribution. Bars represent percentage of particles for each size range and the lines represent the cumulative percentage of the particles.

Table 7.3 Histological classification of retrieved periprosthetic tissue after TDR, THA and TKA revision surgery according to the modified Mirra classification.

Patient number	Chronic inflammatory cells (lymphocytes) ¹	Macrophages ³	Giant cells ³
TDR-1	1+	2+	2+
TDR-2	1+	3+	2+
TDR-3	0	1+	0
TDR-4	0	2+	1+
TDR-5	0	2+	1+
TDR-6	1+	2+	3+
TDR-7	0	2+	1+
TDR-8	0	0	0
TDR-9	1+ ⁴	3+	0
TDR-10	0	3+	2+
TDR-11	0	0	0
TDR-12	1+ ⁴	2+	3+
TDR-13	0	2+	2+
TDR-14	1+ ⁴	0	0
TDR-15	1+	3+	2+
TDR-16	0	0	0
TDR-17	2+ ⁴	2+ ⁴	0
TDR-18	0	1+	0
TDR-19	0	0	0
TDR-20	0	3+ ⁵	1+ ⁴
TDR-21	0	0	0
TDR-22	1+	2+	2+
THA-1	3+	3+	3+
THA-2	2+	3+	1+
THA-3	2+	3+	3+
THA-4	1+	1+	0
THA-5	2+	3+	3+
THA-6	1+	3+	3+
THA-7	2+	3+	3+
THA-8	2+	3+	3+
THA-9	3+	3+	1+
THA-10	2+	2+	0
TKA-1	2+	3+	3+
TKA-2	3+	3+	3+
TKA-3	3+	1+	2+
TKA-4	3+	1+	2+ ⁵

¹ 1+: 1-9 cells/high power field (x500) and/or 1 lymphoid follicle/low power field (x100), 2+: 10-49 cells/high power field (x500) and/or 2-3 lymphoid follicles/low power field (x100), 3+: ≥50 cells/high power field (x500) and/or ≥4 lymphoid follicles/low power field (x100). ² 1+: 1-9 macrophages/high power field (x500), 2+: 10-49 macrophages/high power field (x500), 3+: ≥50 macrophages/high power field (x500). ³ 1+: 1-2 cells/medium power field (x250), 2+: 3-8 cells/medium power field (x250), 3+: ≥ 9cells/medium power field (x250). ⁴ Histology only found in one microscopic field. ⁵ Histology only found in two microscopic fields.

Comparison of the inflammatory cells

An overview of the number and type of inflammatory cells according to a modified Mirra classification is shown in Table 7.3. Lymphocytes were scored 1+ in 8 of 22 TDR

patients, but were scored 2+/3+ in most THA and TKA patients. In the TDR group, macrophages were 0/1+ in 8 patients and 2+/3+ in 14 patients. Macrophages were scored 2+/3+ in all THA patients, except for one patient. There were significantly fewer macrophages in the TDR group compared to THA ($P < 0.01$). In TKA patients macrophages were scored 1+ in 2 patients and 3+ in the other two patients. The number of giant cells was 0/1+ in 14 TDR patients and 2+/3+ in 8 patients. In the THA group they were 0/1+ in four patients, and 3+ in all other samples. Giant cells were scored 2+/3+ in all TKA samples.

DISCUSSION

TDR surgery is increasingly performed as a treatment for degenerative disc disease, with similar success rates at two and five year post-operatively compared to fusion surgery.^{24,39} Recently, it has been demonstrated that PE particles and periprosthetic inflammation can occur after TDR.^{19,20} Nevertheless its clinical relevance is still poorly understood as osteolysis has been rarely observed after TDR.^{19,20} The present study shows that wear mechanisms are comparable to those found in TKA and THA. The observed wear characteristics and histological findings after THA and TKA in this study were consistent with findings from literature.^{7,12-15,25} THA samples showed high numbers of particles $< 6 \mu\text{m}$, mainly contained in macrophages. Particles $> 12 \mu\text{m}$ were less prevalent and therefore, less giant cells were observed. PE particles after TKA had a broad size range, with larger PE particles like fibrils and flakes. As a result, more giant cells were present in TKA compared to THA. In TDR, the size range was comparable to TKA, but the smaller particles predominated, as in THA. In other words, in TDR both macrophages and giant cells were present with relatively higher numbers of macrophages.

Differences in quantity, size and shape of PE particles between TDR, THA and TKA are presumably due to differences in loading and wear mechanisms.²⁶⁻²⁹ Submicron particles in THA appear to be generated by adhesion and abrasion mechanisms, whereas wear conditions in TKA generate larger particles through subsurface delamination, pitting and fatigue cracking.²⁶⁻²⁹ Kurtz et al.¹⁷ described wear and damage mechanisms in PE cores from TDRs similar to those observed in both THA and TKA. In the central, spherical dome region of the TDR cores, microscopic multidirectional scratches were found, comparable to the wear mechanisms observed after THA.¹⁷ Around the rim, extensive plastic deformation and fractures were often observed, produced by endplate impingement and resulting in fatigue damage and fracture, as has been reported in retrieved TKA components. In contrast, the prevailing wear mechanisms in the central dome region were adhesion and abrasion.¹⁷ The similarity with TKA wear patterns at the rim, may explain the broad size range of TDR particles. However, small particles were the most prevalent, probably because the prevailing wear mechanisms at the dome, to THA patterns.

Periprosthetic osteolysis after TDR appears to be a rare phenomenon as it was only seen in one patient in the present study (TDR-10), as described in more detail by van Ooij et al.¹⁹ This single TDR osteolysis patient, does not have an affect on any of the outcomes. To our knowledge, only three other cases of osteolysis potentially attributable to PE wear debris after TDR have been reported.²⁰⁻²² This is in contrast with the clinical experience with vulcanized rubber in a one-piece TDR design known as the Acroflex, which exhibits short-term clinical failure, frequently associated with osteolysis.²¹ In the case of THA and TKA, osteolysis due to PE particles (in metal-on-polyethylene bearings) and cobalt chromium particles (in metal-metal bearings) are well recognized as potential reasons for revision.⁵⁻⁷ Scanning electron microscopy (SEM) showed high concentrations of submicron PE particles in TKA and THA specimens.^{5,13,25,30} These submicron sized particles are known to be the most potent for inducing osteolysis.^{9-11,31} Possibly, submicron sized PE particles are not present in sufficient concentrations to cause osteolysis after TDR. Future research should determine whether submicron sized particles are present after TDR.

Another possible explanation regarding the low frequency of osteolysis in TDR is the osteolysis threshold. The risk of osteolysis appears to increase when the wear penetration rate reaches a critical level.^{17,32} In a review on the association between the PE wear rate and osteolysis, an osteolysis threshold of 0.1 mm/year PE wear in THA was suggested.³² The one patient with osteolysis from the TDR group had a wear penetration rate of 0.14 mm/year, which exceeded the suggested osteolysis threshold in THA.¹⁷ Nevertheless, as this is the only analyzed wear penetration rate of a TDR patient with osteolysis, it will obviously require many more cases of TDR patients to support this hypothesis of an osteolysis threshold in the spine as suggested in the hip. Another theory of osteolysis is the concept of the effective joint space in THA as postulated by Schmalzried et al.³³ This theory states that PE particles generated during wear of the THA, disseminate in the synovial fluid.³³ Depending on the bone-implant contact, the joint fluid and thereby the particles enter the interfaces, the periprosthetic soft tissue and the bone during movement. These areas accessed by the joint fluid become part of the joint space and are then called the effective joint space.³³ When periprosthetic inflammation and bone resorption occur, the effective joint space extends and the process of osteolysis progresses.³³ The absence of a synovial membrane in the intervertebral disc could explain the rarity of osteolysis. It is important to note that the aforementioned osteolysis mechanisms, hypothesized to explain PE particle reactions, may not be relevant to other TDR design and biomaterials. As noted previously, short-term Acroflex failures were frequently associated with osteolysis due to generation of vulcanized rubber debris²¹ and alternative, metal-on-metal artificial discs have been shown to generate metal-ions, which enter the blood stream and circulate systemically.^{34,35} Thus, the findings for osteolysis and particle response in the present study are limited to mobile bearing TDRs containing PE and should not be generalized to TDR designs incorporating other biomaterials.

The PE cores of the Charité TDR have been sterilized by gamma radiation. During this process radicals are being formed, which react slowly with oxygen over time which may have compromised the PE stability.^{2,36} Since 1997, the Charité PE cores were gamma sterilized in first generation barrier packages (N-Vac). Before 1997, the PE cores were gamma sterilized using historical, air permeable packaging by Waldemar Link. The manufacturing of Charité was transferred to DePuy Spine in 2004, and since then the PE cores were sterilized in a vacuum sealed foil pouch (GVF).³⁷ The PE cores in our study have been sterilized by using gamma air or N-Vac, and all were manufactured by Link. No foil pouch barrier packaging PE cores were available in this study. *In vivo* oxidation is a long-term concern in gamma sterilized PE. After implantation the PE comes into contact with oxygen dissolved in body fluids and tissue.³⁷ This amount of oxygen has been proven to be capable of causing oxidation of THA and TKA in less than one decade after implantation.³⁸ In THA, the exposed rims of acetabular liners show frequently oxidation *in vivo*, because the metallic components protect the other areas of the PE bearings.³⁸ Kurtz et al. showed a similar mechanism occurring in TDR, which may explain why oxidation was significantly higher at the rim.³⁷ In these patients oxidation was observed to the same extent in both gamma air and N-Vac sterilized cores.³⁷ Therefore, from the perspective of oxidation, the PE properties of all of the TDRs evaluated in this study can be considered to come from the same population.

One of the limitations of this study is that the cut-off level to detect PE particles was set at a length of 2.05 μm to distinguish between PE and dust particles at the light microscopical level. As a result we were unable to detect submicron sized PE particles, which may be the most bioactive.^{11,31} Therefore, additional research should be performed on submicron sized PE particles. Another limitation is the small number of patients with their relatively high variance. Due to heterogeneity within the groups, it is difficult to correlate patient characteristics and revision reasons with PE wear characteristics and inflammatory reactions. Nevertheless, this is the largest published series worldwide of retrieved TDR prostheses.

The majority of the patients who underwent primary TDR surgery were between 30-50 years old at the time of implantation. This implies that a long life span of the TDR is essential. Charité TDRs show an overall success rate of 57.8% after five years.^{24,39} However, longer follow-up complications are increasingly becoming apparent now.^{19,40} New technologies developed to improve survival of THA and TKA, should also be applied to TDR to create a longer life span. Highly cross linked PE (HXLPE), stabilized by thermal treatments and by vitamin E, has been used with promising initial results in THA and could be promising for wear reduction in TDR, provided concerns regarding *in vivo* oxidation, impingement and rim fracture can be successfully mitigated.⁴¹

CONCLUSION

The present study showed the presence and similarities between PE wear particles and periprosthetic inflammatory cells in TDR, THA and TKA. Both small and large particles are present after TDR revision surgery due to combined THA and TKA wear patterns. The broad range of the length of these PE particles is comparable to TKA. Nevertheless, small particles contained in macrophages were most numerous in TDR, due to domination of wear patterns similar to THA. Although PE wear-related osteolysis is an important cause of revision and reduced longevity in THA and TKA, osteolysis has been rarely observed thus far after TDR. Detailed histomorphologic and radiographic research of future osteolytic TDR patients is necessary to find an explanation for this phenomenon. The similarities between periprosthetic tissue reactions in the different groups may give more insight in the clinical relevance of PE particles and inflammatory cells in the lumbar spine. Future TDR retrieval cases with an index surgery after 2004 are necessary to establish insight in PE wear particles and periprosthetic tissue reactions of Charité TDR PE components stored within second generation (GVF) barrier packaging.

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CHAPTER 8

**Submicron sized ultra-high molecular weight
polyethylene wear particle analysis from revised SB
Charité III total disc replacements**

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ABSTRACT

Submicron sized particles are frequently observed in retrieved total hip and knee periprosthetic tissues and appear to be critical in the activation of the phagocytic inflammatory response. In this paper the concentration, size and shape of ultra-high molecular weight polyethylene (UHMWPE) wear particles between 0.05 and 2.00 μm were determined after isolation from periprosthetic tissues from retrieved lumbar SB Charité III total disc replacements (TDR) using scanning electron microscopy (SEM). For comparison, UHMWPE wear particles were isolated from γ -radiation-air sterilized total hip arthroplasty (THA) revision tissues. The mean concentration of UHMWPE particles in TDR tissues was $1.6 \times 10^9 \text{ g}^{-1} \text{ tissue}$ (range 1.3–2.0), which was significantly lower than the concentration of $2.3 \times 10^9 \text{ g}^{-1}$ THA revision tissue (range 1.8–3.2) ($P=0.03$). The mean particle size (equivalent circular diameter: TDR, 0.46 μm ; THA, 0.53 μm , $P=0.60$) and mean shape were comparable between TDR and THA (aspect ratio: TDR, 1.89; THA, 1.99, $P=0.35$; roundness: TDR, 0.58; THA, 0.56, $P=0.35$). However, the TDR particles tended to be smaller and more round. Although no correlations were found between visible damage to the UHMWPE core and the concentration or shape of the UHMWPE particles, a positive correlation was found between increasing particle size and increasing rim penetration of the TDR core ($P=0.04$). The presence of UHMWPE particles of similar size and shape in TDR tissue, albeit lower in concentration, might explain why, unlike THA, pain rather than osteolysis is the major reason for revision surgery.

INTRODUCTION

For patients who suffer from degenerative disc disease lumbar fusion of the affected vertebral segment has been the standard treatment. However, studies have shown that fusion of a single level results in an accelerated rate of degeneration in adjacent discs and vertebral levels due to altered biomechanics.^{1,2} Alternatively, total disc replacement (TDR) achieves both a resolution of pain and preserves the motion segment of the functional spine unit, and thus represents an appealing surgical alternative.^{3,4} The SB Charité III (Link/De Puy, Germany/USA), the first FDA approved TDR device in the USA, includes an ultra-high molecular weight polyethylene (UHMWPE) core articulating between two cobalt chromium (CoCr) endplates.⁵ Currently the short- and midterm clinical results of the Charité TDR are at least equivalent to the clinical outcomes of lumbar interbody fusion, with success rates of 65.2% and 57.8% at 2 and 5 years follow-up, respectively.^{3,6-8} Nevertheless, as several studies have identified a low quality of evidence supporting the efficiency of TDR over fusion, the long-term effectiveness of this relatively new medical device compared with lumbar fusion remains unclear.⁹⁻¹¹

During the development of TDR component technology a combination of biomaterials and design concepts were adopted from devices used in total hip arthroplasty (THA) and total knee arthroplasty (TKA). However, based on previous clinical experience with THA and TKA, the accumulation of UHMWPE wear debris is implicated in the development of inflammatory reactions that contribute to osteolysis and aseptic implant loosening.¹²⁻¹⁷ The extent of this inflammatory response is affected by several characteristics of the UHMWPE wear debris, which include particle concentration (number per gram of tissue), size and shape.¹⁸⁻²¹ Smaller particles tend to be the most biologically active, as is also true for elongated particles compared with round or spherical particles.^{17,18,22}

While osteolysis and loosening represent the most frequent reasons for revision surgery of THA and TKA implants²³⁻²⁷, the development of osteolysis around TDR is rarely observed.²⁸⁻³² Initially it was thought that the generation of substantial amounts of UHMWPE wear debris in the spine was unlikely due to a limited range of motion and the absence of a synovial joint.^{5,31} These views were based on an *in vitro* study by Serhan et al.³¹, showing only minimal wear debris generation after 10,000,000 cycles. However, in a recent immunohistological study we identified the concomitant presence of UHMWPE particles ($\geq 2.05 \mu\text{m}$), phagocytic cells and pro-inflammatory cytokines in periprosthetic tissues around retrieved TDR.³³ The study was limited by the inability of polarized light microscopy to quantify the full range of submicron sized UHMWPE particles. Therefore, the aims of the present study were to determine the concentration, size and shape of UHMWPE wear particles between 0.05 and 2.00 μm in periprosthetic tissues from retrieved TDR, to compare these findings with wear debris isolated from THA revision tissues, and to identify correlations between the characteristics of TDR wear debris and visible damage to the UHMWPE core.

We hypothesize that UHMWPE wear debris generation from TDR implants should be minimal and if generated the characteristics of the particles should differ from those arising from THA implants. To determine whether these hypotheses are true we isolated and characterized wear debris from TDR and THA revision tissues.

MATERIALS AND METHODS

Implant characteristics

In total 34 SB Charité III TDR were collected from 29 patients during revision surgery at the Maastricht University Medical Center. In a previous study 16 available patient tissues were evaluated for the presence of inflammation and >2.05 µm UHMWPE particles.³³ Of these, we selected tissues from five single level TDR (2 male, 3 female) implanted with non-coated SB Charité III manufactured by LINK to evaluate the size, shape and number of <2 µm UHMWPE particles using scanning electron microscopy (SEM). The surface damage to the corresponding UHMWPE implant components was also evaluated. The five patients included in the present study showed similar clinical variables and tissue responses as the 11 TDR cases that were reported in a previous study (Table 8.1).³³ Periprosthetic fibrous tissue samples were obtained from random locations relative to the implant at the time of revision surgery. Revision of these five patients was indicated after 9 years (range 6–12 years) due to persistent back and leg pain (Table 8.2). The mean age of the patients at the time of primary surgery was 37 years (range 33–46 years). Separately, UHMWPE particles were evaluated in tissue samples from single TDR revised for osteolysis. Since the development of osteolysis around TDR is rarely observed, we separately compared this case to the control THA revised for osteolysis (detailed below).

Periprosthetic tissues were obtained from the Maastricht Pathology Tissue Collection. Collection, storage and use of tissue and patient data were performed in agreement with the “Code for proper secondary use of human tissue in the Netherlands” (<http://www.fmwv.nl>). All procedures were performed in accordance with the Institutional Review Board guidelines of Drexel University.

Table 8.1 Comparison of the 5 non-coated single-level TDRs included in the present study and the 11 cases from the original study of the first 16 patients³² (± standard error of the mean).

	5 non-coated single TDRs (included)	Residual 11 TDR cases from the original cohort ³² (excluded)	P-value
Age at implantation (year)	39.6 ± 2.8	42.0 ± 2.1	0.61
Gender ♀- ♂	3 – 2	9 – 2	0.37
Implantation time (years)	9.2 ± 1.0	7.5 ± 1.3	0.25
Mean number of UHMWPE particles/mm ² (≥2.05 µm)	114.0 ± 52.8	280.0 ± 100.8	0.78
Macrophages (Mirra classification 0 - 1+ - 2+ - 3+)	0 – 1 – 3 – 1	2 – 0 – 4 – 5	0.54
Giant-cells (Mirra classification 0 - 1+ - 2+ - 3+)	2 – 2 – 0 – 1	4 – 1 – 4 – 2	0.60

Table 8.2 Summary of patient and clinical variables for TDRs and THAs.

Implant number	Sex	Age at implantation	Prosthesis	Revision reason	Implantation time (years)	Air/ inert	Level	Endplate size
TDR								
Maa003	m	46	Charité (LINK)	Subsidence, back and leg pain	6	Unknown	L4-5	3
Maa009	m	39	Charité (LINK)	Pain due to severe facet joint degeneration L4/L5 and degeneration disc L1-2 and L3-4	10	Air	L4-5	3
Maa010	f	34	Charité (LINK)	Persisting pain after failed posterior fusion	8	Unknown	L5-S1	3
Maa013	f	33	Charité (LINK)	Instability/Retrolisthesis L1-2/L2-3; Pseudo-arthrosis L4-5; Anterior position & possible wear L3/L4	12	Air	L3-4	2
Maa018	f	33	Charité (LINK)	Persistent lumbar pain and right leg pain; disc degeneration L3/L4	10	Air	L4-5	3
THA								
CW/H002	m	67	Zimmer HGPII	Polyethylene wear, Osteolysis	13	Air	n/a	n/a
RIH120	f	62	Biomet Hexloc	Polyethylene wear, Osteolysis	15	Air	n/a	n/a
RIH426	f	43	Biomet Hexloc	Polyethylene wear, Osteolysis	14	Air	n/a	n/a
RIH134	m	Unknown	Biomet Hexloc	Polyethylene wear, Loosening (Femoral)	11	Air	n/a	n/a
RIH369	f	45	Biomet Hexloc	Polyethylene wear, Loosening (Acetabular)	13	Air	n/a	n/a
P-value	1.00	0.05			0.02			

L, lumbar vertebrae; HGP, Harris-Galante Porous

Controls

The TDR tissue samples were compared with periprosthetic fibrous tissue from five revised metal-on-UHMWPE THA, which were revised after 13 years (range 11–15 years) due to wear and/or osteolysis (Table 8.2). These controls were chosen for comparison based on the γ -irradiation-air sterilized UHMWPE core material used in these devices as well as the SB Charité III design. The control THA group had a comparable gender distribution and the patients were of similar age at implantation ($P=1.00$ and $P=0.05$, respectively) as the TDR group. However, due to the extended longevity of THA implants the implantation time was significantly longer in the THA group compared with the TDR group ($P=0.02$) (Table 8.2).

Tissue digestion protocol

The tissue samples were fixed in 10% phosphate-buffered formalin and the bone tissue was subsequently decalcified. During decalcification the specimens were kept in a 3.5% sodium formate and 25% formic acid solution³⁴, until they were soft enough and could be embedded in paraffin. Particle isolation and characterization was performed using methods modified from Margevicius et al.¹⁵. Using polarized light microscopy several areas of the fibrous tissue that were thought to be representative of tissue containing UHMWPE particles were removed from the paraffin block. This tissue was deparaffinized in 10 ml of xylene overnight at room temperature and washed twice in xylene and twice in 100% ethanol for 3 min each. After drying for 2 h at room temperature 0.02–0.03 g of tissue were placed in a polypropylene tube and digested in 5 ml of 65% HNO_3 at room temperature for 24 h. After the first 24 h the tubes were agitated and left to digest for an additional 24 h.

Following digestion the solutions containing UHMWPE wear debris were thoroughly mixed with a G560 vortex (Scientific Industries, Bohemia, NY) for three 30 s intervals. Finally the tubes were placed in an ultrasonic bath (Cole-Parmer, Vernon Hills, IL) for 2 min to achieve a uniform particle dispersion. Subsequently the sample was vacuum filtered through a polycarbonate membrane with a pore size of 1.0 μm (Whatman, Billerica, MA) and the filtrate containing submicron particles was collected and saved. After filtration the membrane was washed with 10 ml of fresh 65% HNO_3 , which was added to the membrane surface for 10 min and subsequently pulled through by vacuum. Finally, using a separate sidearm flask, this washing process was repeated with methanol. To prevent particle agglomeration the filtrate containing submicron particles was diluted with 15 ml of methanol containing 2% Nonidet P-40® (NP40 substitute) (AppliChem GmbH, Darmstadt, Germany), a non-ionic surfactant. The solution containing surfactant was mixed with a vortex for three 30 s intervals and subsequently placed in an ultrasonic bath for 2 min to achieve a uniform particle dispersion and to further reduce agglomeration. After sonication the samples were immediately filtered through a membrane with a pore size of 0.05 μm . As with the first membrane, the second polycarbonate membrane was sequentially washed with

10 ml solutions of 65% HNO_3 followed by methanol, which were again collected in separate side-arm flasks. Based on the thorough digestion of small quantities of tissue, centrifugation steps were not employed during particle isolation, however, this may require modification for larger tissue samples. Each membrane was then dried for 2 h at room temperature and prepared for SEM.

Scanning electron microscopy

Polycarbonate membranes with isolated UHMWPE wear debris were fixed onto aluminum stubs with double-sided carbon tape and sputter coated with a 5 nm thick layer of platinum/palladium using a 208 HR vacuum sputter coater (Cressington, Watford, UK). This method of sample preparation was necessary to eliminate sample drift and/or damage by the electron beam at high magnifications. Coated samples were inserted into an XL30 environmental scanning electron microscope (FEI/Phillips, Hillsboro, OR) equipped with a Schottky field-emission gun and an energy-dispersive X-ray detector (EDAX, Mahwah, NJ) to visualize UHMWPE wear debris. Imaging was performed at a working distance of 12 mm and a beam intensity of 5 kV. All sample preparation and imaging were performed in the Drexel University Centralized Research Facilities.

After demonstrating a homogeneous distribution of particles the polycarbonate membranes with a pore size of 1.0 μm were imaged at magnifications of 500 $\times$ and 1000 $\times$; five and 10 images were collected, respectively. Separately, polycarbonate membranes with a pore size of 0.05 μm were imaged at a magnification of 12,000 $\times$; 10 images were collected from each of three separate regions. Altogether, the membranes contained a minimum of 1000 particles in the size range 50–2000 nm.

Particle analysis

Image analysis of SEM micrographs was initially performed using a gray scale level threshold in Photoshop (Adobe, San Jose, CA). Subsequently, using a scale bar from each micrograph, the individual particle areas and dimensions were determined using a custom macro in NIH ImageJ (National Institutes of Health, Bethesda, MD). The resulting areas and dimensions were used to characterize particle concentration, size (equivalent circular diameter) and shape (aspect ratio, roundness) based on guidelines for particle analysis outlined in ASTM F1877 (Table 8.3).³⁵

Validations

To validate the particle isolation techniques two tissue samples (0.02–0.03 g) from primary spine surgery were selected. Control tissues were processed using the digestion and imaging methods detailed above.

To determine the effect of using a small tissue weight 0.025 and 0.25 g samples were processed using the digestion and imaging methods detailed above. After image processing the particle concentrations were determined for each sample.

To validate methods for evaluating particle morphology we obtained reference standard UHMWPE particles (RM8385) generated by rubbing a γ -irradiated UHMWPE pin against a textured surface in a reciprocating pin-on-disk system (National Institute of Standards and Technology, Gaithersburg, MD). A solution containing UHMWPE particles with a nominal diameter of 7 μm was vacuum filtered through a polycarbonate membrane with a pore size of 1 μm . Particles were analyzed using the imaging and image processing methods described above and the values obtained for particle size were then compared with values provided in the reference standard. The mean difference ($\pm\text{sem}$) in the percentage of particles was 1.3% (± 0.4) across all size ranges (Figure 8.1).

Table 8.3 Summary of wear particle characteristics.

Parameter	Equation	Definition
ECD (μm)	$2*\text{sqrt}(A/\pi)$	Diameter of a circle with an area equivalent to the particle area (A) ³⁴
AR (unitless)	$d_{\text{max}}/d_{\text{min}}$	Ratio of major (d_{max}) to minor diameter (d_{min}) ³⁴
R (unitless)	$(4*A)/(\pi*d_{\text{max}}^2)$	Measure of circularity varying from zero to one (perfect circle) ³⁴

ECD, equivalent circular diameter; AR, aspect ratio; R, roundness; A, particle area.

Figure 8.1 Histogram of the particle size from a validation sample as compared to the NIST reference standard (RM8385). The mean % difference ($\pm\text{sem}$) across all size ranges was 1.3 $\pm$ 0.4.

Visible UHMWPE damage

The wear patterns of each retrieved polyethylene core was analyzed at the rim and dome. Dome and rim penetration measurements were performed in these five cores using a calibrated digital micrometer (± 0.001 mm accuracy).^{36,37}

Statistical analysis

Sample size analyses were performed using the THA control samples; a twofold decrease in particle concentration was detected at a power of 80% and a level of significance of 0.05. Analyses were performed using SPSS 16.0. The Mann–Whitney *U*-test was used to evaluate differences between the TDR and THA samples. The relationships between surface damage and the characteristics of the submicron UHMWPE particles were analyzed using the Spearman ρ correlation. Significance was assumed at $P < 0.05$.

RESULTS

To determine UHMWPE particle concentrations we isolated and characterized wear debris in periprosthetic tissues from five TDR and five THA revision cases. Over 1000,000,000 wear particles per gram of tissue were present in all five TDR patient samples. The mean TDR UHMWPE particle concentration was $1.6 \times 10^9 \text{ g}^{-1}$ (range 1.3–2.0). Although present, the amount was significantly lower than the concentration of particles in THA periprosthetic tissues ($2.3 \times 10^9 \text{ g}^{-1}$, range 1.8–3.2) ($P=0.03$, power=0.6) (Table 8.4). For the separately evaluated TDR case revised for osteolysis an elevated concentration of UHMWPE particles ($2.6 \times 10^9 \text{ g}^{-1}$ tissue) was detected that resembled the THA osteolytic revision concentrations.

Comparing particle size, no differences were observed between the mean equivalent circular diameter for TDR and THA particles ($P=0.60$). The mean equivalent circular diameter was $0.464 \pm 0.050 \text{ }\mu\text{m}$ and $0.529 \pm 0.055 \text{ }\mu\text{m}$ for TDR and THA, respectively. Although the overall particle size was similar for both groups, significantly more TDR particles were observed in the 50–200 nm size range ($P=0.04$), whereas particles in the 800–1000 and 1000–1250 nm size range were more frequent in THA tissues ($P=0.03$ and $P=0.01$, respectively). For both groups the highest frequency of particles was in the 50–200 nm size range.

Analysis of UHMWPE wear particles from TDR and THA revision tissues revealed a wide range of particle shapes (Figure 8.2A–D). Overall, no differences were observed for the mean particle aspect ratio between the two groups ($P=0.35$); TDR 1.890 ± 0.044 and THA 1.987 ± 0.070 . Although the mean aspect ratio was similar for both groups, differences were observed in the individual aspect ratio ranges. For TDR particles with an aspect ratio between 1.25–1.50 were more frequently observed ($P=0.04$), whereas THA particles were increased in the 2.5–2.75 range ($P < 0.05$). For both groups the

particle aspect ratio distribution reached a peak at 1.25–1.50, which rapidly dropped off below 1.25 and declined gradually above 1.5.

Table 8.4 Summary of UHMWPE particle concentration, size and shape in TDR and THA.

Implant number	Tissue weight (gram)	Number of particles ($\times 10^9 \text{ gram}^{-1}$)	Particles per year ($\times 10^9 \text{ gram}^{-1} \text{ yr}^{-1}$)	ECD mean $\pm$ sem, median	Aspect ratio mean $\pm$ sem, median	Roundness mean $\pm$ sem, median
TDR						
Maa003	0.0267	1.794	0.287	0.481 $\pm$ 0.004, 0.376	2.062 $\pm$ 0.011, 1.864	0.536 $\pm$ 0.002, 0.536
Maa009	0.0238	1.488	0.146	0.476 $\pm$ 0.007, 0.360	1.870 $\pm$ 0.013, 1.709	0.579 $\pm$ 0.003, 0.585
Maa010	0.0223	1.990	0.235	0.334 $\pm$ 0.012, 0.266	1.848 $\pm$ 0.024, 1.652	0.590 $\pm$ 0.006, 0.605
Maa013	0.0224	1.523	0.119	0.633 $\pm$ 0.007, 0.521	1.859 $\pm$ 0.011, 1.670	0.585 $\pm$ 0.003, 0.599
Maa018	0.0207	1.308	0.124	0.396 $\pm$ 0.009, 0.299	1.809 $\pm$ 0.018, 1.647	0.601 $\pm$ 0.004, 0.607
Mean $\pm$ sem		1.621 $\pm$ 0.121	0.182 $\pm$ 0.034	0.464 $\pm$ 0.050	1.890 $\pm$ 0.044	0.578 $\pm$ 0.011
THA						
CWH002	0.0252	2.262	0.173	0.618 $\pm$ 0.009, 0.376	1.903 $\pm$ 0.009, 1.736	0.570 $\pm$ 0.002, 0.576
RIH120	0.0246	2.481	0.159	0.701 $\pm$ 0.004, 0.564	2.002 $\pm$ 0.007, 1.791	0.552 $\pm$ 0.001, 0.558
RIH426	0.0240	3.237	0.294	0.468 $\pm$ 0.002, 0.399	1.785 $\pm$ 0.005, 1.678	0.594 $\pm$ 0.001, 0.596
RIH134	0.0263	1.798	0.127	0.407 $\pm$ 0.005, 0.307	2.039 $\pm$ 0.015, 1.791	0.553 $\pm$ 0.003, 0.558
RIH369	0.0246	1.881	0.145	0.454 $\pm$ 0.011, 0.344	2.207 $\pm$ 0.037, 1.810	0.551 $\pm$ 0.006, 0.555
Mean $\pm$ sem		2.332 $\pm$ 0.258	0.180 $\pm$ 0.030	0.529 $\pm$ 0.055	1.987 $\pm$ 0.070	0.564 $\pm$ 0.008
<i>p</i> -values		0.03	0.60	0.60	0.35	0.35

ECD, equivalent circular diameter; sem, standard error of the mean.

For roundness no differences were observed between TDR and THA particles ($P=0.35$). Overall, the mean particle roundness was 0.578 ± 0.011 and 0.564 ± 0.008 for TDR and THA, respectively. Similar to the findings for equivalent circular diameter and aspect ratio, differences between TDR and THA particle roundness were only observed in individual ranges. Specifically, TDR particles were more frequently observed in the range 0.75–0.80 ($P=0.02$), and in general were less fibrillar, whereas THA particles were increased in the range 0.35–0.40 ($P=0.01$). For both groups the particle roundness distributions reached a maximum at 0.60–0.65, which declined at a similar rate below 0.60 and above 0.65. Taken together, these findings suggest that particle size (Figure 8.3A) and shape (Figure 8.3B-C) tended to be smaller and more granular (round) for TDR compared with THA particles.

In the assessment of surface damage on retrieved UHMWPE components dome as well as rim penetration patterns showed large variations between patients (Table 8.5). Due to this variation the only positive correlation between regional component damage and UHMWPE particle characteristics was an increase in particle size with increasing linear rim penetration (mm) ($P=0.04$).

Figure 8.2 Representative ESEM images of UHMWPE wear debris from (A,B) TDR and (C,D) THA cohorts (magnification 12,000x).

Table 8.5 Summary of Visible Damage on the UHMWPE Core.

Implant number	Dome penetration (mm)	Dome penetration rate (mm yr ⁻¹)	Rim penetration (mm)	Rim penetration rate (mm yr ⁻¹)
Maa003	0.1080	0.0173	0.418	0.0669
Maa009	0.5410	0.0529	0.085	0.0083
Maa010	0.3706	0.0437	0.019	0.0022
Maa013	0.3572	0.0280	0.103	0.0080
Maa018	0.3332	0.0314	0.059	0.0055
Mean (± sem)	0.3420 ± 0.0691	0.0347 ± 0.0062	0.1368 ± 0.0717	0.0182 ± 0.012

mm, millimeter

Figure 8.3 Histogram of the **A)** equivalent circular diameter, **B)** aspect ratio, and **C)** roundness of TDR and THA UHMWPE wear debris. Bars represent the mean percentage of particles within each size/shape range ($\pm$ sem).

DISCUSSION

Based on clinical experience with UHMWPE bearings in THA and TKA studies, it is known that UHMWPE wear particles play a critical role in the inflammatory responses that contribute to the development of osteolysis and, ultimately, the need for revision surgery.^{12,14-18} However, in TDR, where osteolysis is rarely observed, the inflammatory role of UHMWPE is uncertain, in part because the characteristics of TDR wear particles *in vivo* have not been clearly defined.³³ Therefore, the current study was performed using SEM to determine: (1) the concentration, size and shape of UHMWPE wear particles between 0.05 and 2.00 μm in periprosthetic tissues from retrieved TDR; (2) to compare these findings with wear debris isolated from THA revision tissues; (3) to identify correlations between the characteristics of TDR wear debris and visible damage to the UHMWPE core.

There are some limitations in the current study. First, a subset of five patients with non-coated and single level TDR was selected from a previous study.³³ This selection was chosen to eliminate potential complications of adjacent level TDR and wear debris generation from coated metal surfaces. Moreover, no differences were observed between clinical variables or tissue responses of these five patients, compared with the other 11 patients from our previous study. Second, although this is a representative subset of TDR revisions, the revised components exhibited variable amounts of surface damage. As component damage was not a factor in patient selection the characteristics of the UHMWPE wear particles are inclusive of a wide range of TDR component failure modes. Third, a 0.05 μm polycarbonate filter was chosen based on the environmental scanning electron microscopy (ESEM) study by Scott et al.³⁸ showing that only a small percentage (2.8%) of THA particles were smaller than the 0.05 μm pore size.³⁸ Thus it is unlikely that the method of sample preparation contributes to an under- or overestimate of the concentration, size or shape of wear particles present in the current TDR and THA revision tissues. Fourth, the TDR and THA wear particles were obtained from UHMWPE that was γ -irradiated in air, a historical sterilization method that is no longer employed for spine and orthopedic implants. Nevertheless, the particle data reported here provide a crucial, and heretofore unavailable, reference point for future studies of conventional γ -irradiation-inert sterilized UHMWPEs that are currently used for contemporary total disc arthroplasty.

The assumption that UHMWPE wear debris generation from TDR implants would be minimal is not supported by our findings. The results from the present study showed a UHMWPE particle concentration of 1.6×10^9 particles g^{-1} tissue in the TDR group. For this reason future studies will require additional samples to achieve higher statistical power.

Although few studies have evaluated the presence of wear debris in TDR revision tissues, case studies of TDR component wear and our previous work highlight the potential for wear particle accumulation.^{32,33} In the present study γ -irradiation-air

sterilized TDR component revision tissues contained $1.3\text{--}2.0 \times 10^9$ particles g^{-1} tissue. The concentration of UHMWPE wear particles in γ -irradiation-air sterilized THA component tissues was more variable ($1.8\text{--}3.2 \times 10^9$ particles g^{-1} tissue), but consistent with previous reports.^{14,39} Of note, the implantation time was longer for THA compared with TDR, so it is unclear whether an equivalent concentration of particles would be generated if the device remained functional for a longer period of time.

For the single case of TDR osteolysis revised in our hospital we noted an elevated concentration of UHMWPE particles ($2.6 \times 10^9 \text{ g}^{-1}$). Thus, based on studies showing an osteolytic threshold for wear debris in THA revision cases^{40,41}, the presence of an elevated number of particles after only 6 years implantation introduces the possibility of an osteolytic threshold in the spine. If a linear wear rate is assumed, and based on the similar calculated number of UHMWPE particles generated annually for TDR ($0.182 \times 10^9 \text{ g}^{-1} \text{ year}^{-1}$) and THA ($0.180 \times 10^9 \text{ g}^{-1} \text{ year}^{-1}$) ($P=0.60$), it is conceivable that if TDR implantations were extended the number of particles would reach equivalent concentrations as those observed in THA osteolytic revision cases.

In our previous study we evaluated the presence of UHMWPE wear particles $>2 \mu\text{m}$ in TDR revision tissues.³³ 15 of the 16 patients had polarized light detectable wear debris, which ranged from 3.8 to 15.9 μm in length. As an extension of the previous study, all five tissues selected for ESEM analysis contained predominantly submicron wear debris (0.05–2 μm), which are considered to be more biologically active. Similarly, all five THA revision tissues contained wear debris in this size range, and particle sizes of the THA UHMWPE particles (mean 0.53 μm) were comparable with previous studies.^{14,17,24,42} Taking into account the use of a 0.05 cut-off filter in the present study, the mean particle size range for the THA tissues (0.41–0.7 μm) was also comparable with previous reports of mean values ranging from 0.38 to 0.78 μm .^{12,14,17,39} In addition, based on a particle size cut-off of 0.1 μm , Howling et al.²⁴ showed that $>80\%$ of particles from THA γ -irradiation-air sterilized liners were between 0.1 and 0.5 μm , which agrees with the value of approximately 80% observed for THA in the current study.²⁴

In general, the morphology of UHMWPE particles from TDR tended to be more rounded compared with THA particles. For both TDR and THA the particle morphologies were predominantly globular, with the mean aspect ratio values from individual patients ranging from 1.8 to 2.2. Fibrillar particles were also observed in both groups, but to a lesser extent. These findings were consistent with the determination of aspect ratio from previous studies of γ -irradiation-air sterilized THA particles, for which the mean was typically between 1.6 and 2.3.^{24,39,43} For particle roundness, which was calculated based on the parameter definition specified by the ASTM, mean values ranged from 0.54 to 0.60 for both TDR and THA. Numerically the roundness parameter specified by the ASTM is identical to the inverse of the aspect ratio. Thus, the mean values of roundness in the current study were also consistent with previously published data, which ranged from 0.42 to 0.63.^{24,39,43}

In THA UHMWPE wear patterns involve micro-adhesion and micro-abrasion, whereas wear patterns in the TDR core involve combined wear damage mechanisms. Specifically, in the central TDR dome region adhesive/abrasive wear mechanisms were comparable with those of THA, whereas at the rim wear patterns included a combination of micro-adhesion and micro-abrasion and fatigue, which is similar to the wear observed in TKA.⁴⁴ Surface damage to the UHMWPE core was not correlated with either particle concentration or shape. The current retrieved UHMWPE TDR cores showed large inter-individual differences in adhesive/abrasive wear patterns at both the dome and rim. Despite this variability, patients with a higher rim penetration showed a significant increase in mean wear particle size or equivalent circular diameters ($P=0.04$).

Traditionally, the presence of submicron UHMWPE wear debris is implicated in the activation of a biological cascade associated with the onset of osteolysis at the bone–implant interface and, ultimately, aseptic implant loosening.^{18,24,45} This response involves a number of cell types and the subsequent release of various cytokines and factors (e.g. tumor necrosis factor- α (TNF- α), interleukin 1 (IL-1), interleukin 6 (IL-6) and prostaglandin E₂ (PGE₂)) that promote adverse biological responses and/or bone loss.^{16,46,47} In addition to particle size, particle concentration and shape can affect the release of osteolytic cytokines.^{18,43,48,49} In tissues around TDR these cytokines may contribute, either additionally or in a dualistic manner, to the development of neuroinflammation-induced pain, as an inflammatory response was observed in all five TDR patient tissues revised for pain.³³ Specifically, TNF- α , IL-1, IL-6 and PGE₂ can induce peripheral sensitization of sensory neurons or induce pain indirectly by recruiting immune cells and up-regulating the release of pain mediators in the affected area.^{50,51} Thus the full repertoire of inflammatory responses to wear debris in the spine has not been established.

CONCLUSION

TDR revision tissues contained over a billion wear particles per gram, and although lower than THA tissue concentrations, this represents a substantial load within the spinal tissue. Moreover, despite 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 THA. Taken together, these findings for historical γ -irradiation-air sterilized UHMWPE implicate wear debris as an important factor contributing to the need for TDR revision surgery. In THA wear debris initiates an inflammatory response that directly contributes to the development of osteolysis. It is therefore conceivable that the lower TDR particle concentrations may account for the infrequent observation of TDR revision surgery for osteolysis, but nonetheless initiate neuro-inflammation. Additional work is necessary to understand the contribution of particle-induced inflammation in the development of pain in the spine.

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CHAPTER 9

General discussion

In recent years, lumbar total disc replacement (TDR) is frequently used as surgical treatment in patients with degenerative disc disease (DDD). It is important to increase our knowledge about the long-term durability of a lumbar TDR. Most patients are between 30-50 year when the TDR is implanted. The *in vivo* durability of a TDR, however, is unknown. Studies on the longevity of a TDR may enable us to predict the clinical success of these relatively new medical devices. And if a TDR does fail, it is important to know if surgical procedures are effective and safe.

This chapter contains an outline of the main findings and conclusions of this thesis. Furthermore, the indications, procedure and findings of revision surgery are described. Finally, the implications of our findings and recommendations for future research will be addressed.

MAIN FINDINGS

In this thesis, we studied two surgical revision techniques in patients with a failed SB Charité III TDR. We observed that it was feasible to remove an L5-S1 TDR in a similar way to its implantation, and an anterolateral approach from the left side was performed to remove a TDR at the level L4-L5 or higher. In both surgical strategies, we found that vessel injuries are important inherent risks (Chapter 2). The mean visual analogue scale (VAS) and oswestry disability index (ODI) scores were not significantly different at 1 year follow-up (Chapter 3) and at mid-term follow-up (Chapter 4), when the TDR was removed combined with instrumented posterolateral fusion as compared to posterolateral instrumented fusion alone. However, a clinically relevant improvement of $\geq 25\%$ in VAS scores was present in 47% in the removal group versus 27% in the fusion group at mid-term follow-up. In both follow-up studies it was concluded that the potential of substantial intra-operative complications of TDR removal should be carefully weighed up against the possible benefits of TDR removal surgery.

In Chapter 5, a reliable method was designed to measure and classify subsidence of an L4-L5 TDR using plain radiographs. A threshold for the minimum area of the bony endplate that should be covered by the TDR was found to reduce the risk of subsidence.

Periprosthetic samples of fibrous tissues, collected during revision surgery of the TDR, were analyzed using light microscopy and polarized light microscopy (Chapter 6), demonstrating the presence of micron-sized ultra high molecular weight polyethylene (UHMWPE) wear particles and periprosthetic inflammatory reactions around failed TDRs. The size range of the UHMWPE particles in TDR was comparable to those observed in total knee arthroplasty (TKA). However, the smallest particles were the most numerate similar to those in total hip arthroplasty (THA). In TDR both macrophages and giant cells were present with higher concentrations of macrophages, comparable to THA (Chapter 7). Finally, in Chapter 8 the presence of

submicron-sized UHMWPE particles using scanning electron microscopy (SEM) is described. Although the mean submicron particle size and shape were comparable to those observed in revised THA, lower concentrations of UHMWPE particles were present in TDR.

INDICATIONS FOR REVISION SURGERY

As with all medical devices, TDR implants are subject to short- and long-term failure. The incidence of reoperations due to failures of the Charité TDR has been reported to be between 2 and 14%.¹⁻⁶ Post-operative implant failures can be related to (i) bone-implant fixation, (ii) bone failure around the TDR, and (iii) wear debris.

Ad. i.

The first generation of the SB Charité III TDR was non-coated, therefore the potential for bone ingrowth into the metal endplate was not possible. To improve the bone-implant fixation, starting in 1998, the endplates of the Charité TDR were hydroxyapatite coated.^{7,8} In our series, these hydroxyapatite coated endplates were somewhat more difficult to remove. However, osteointegration of the bone into the implant was never observed in our series. An unsuccessful bone-implant fixation could result in migration of the TDR. Both anterior and posterior migration of the TDR was observed in a subgroup of our patients. Migration of the TDR may block the lumbar segment, thus eliminating one of the purposes of a TDR: (near) normal range of motion of the lumbar segment.⁹⁻¹¹

Ad. ii.

Bone failure around the TDR is another possible failure mechanism. The metal endplate of the TDR should engage the complete bony vertebral endplate in order to prevent subsidence. For this reason multiple TDR sizes, angles and disc heights are available on the market. Subsidence could occur as a result of asymmetric implantation (or lateral migration of the TDR) or of undersizing. Our radiographic evaluations showed that approximately 50% of the patients with a failed TDR showed minor or major subsidence of the TDR into the vertebral bony endplate. However, Chapter 2 demonstrates that in 4 patients the subsidence was not related to asymmetric implantation or under sizing. Intra-operative endplate violation or a reduced bone quality are possible explanations that a perfectly implanted TDR may subside as well. Osteoporosis as confirmed by DEXA scans is one of the exclusion criteria for TDR implantation. With finite element (FE) analysis studies, the effect of small differences in bone quality on the development of subsidence can be further determined. Subsidence can change the range of motion of the vertebral segment,

which alters forces acting on the facet joints of the operated segment and adjacent segments.¹²

Ad. iii.

Finally, implant wear is also studied as a third failure mechanism. Although it was initially presumed not to be a clinically concern due to limited intervertebral joint motion in the lumbar spine and the lack of a synovial membrane in the disc,¹³ the formation of UHMWPE wear debris and periprosthetic tissue reactions have been proven and appear to be of clinical relevance. Wear debris is a well known phenomenon in THA and TKA that ultimately may lead to revision surgery due to osteolysis and aseptic loosening.¹⁴⁻¹⁶ Although osteolysis after TDR has rarely been reported as yet,^{5,17-19} the TDR osteolysis case in our series which was revised after 6.5 years, indeed showed the highest concentration of UHMWPE particles using polarized light microscopy ($\geq 2.05 \mu\text{m}$) as well as scanning electron microscopy (SEM, 0.05-2.00 μm). Submicron-sized UHMWPE particles are known to be the most potent for inducing osteolysis in THA and TKA patients.²⁰⁻²² Future research should determine whether there is an osteolysis threshold in TDR patients by studying fibrous tissue samples from revised TDR patients in more detail using normal and polarized light microscopy and SEM, furthermore the UHMWPE core should be analyzed to study different wear patterns.

Surface damage of the UHMWPE core of the Charité TDR has been studied using MicroCT.²³ The dome exhibited burnishing, which is consistent with the adhesion and abrasion wear patterns as seen in samples from retrieved THA. Around the rim, radial and transverse cracking patterns were observed more similar to those in TKA.^{8,24} Furthermore, oxidation of the UHMWPE core may reduce the durability of the TDR. Packaging changed in 1997 from air to inert, to prevent oxidation during shelf storage. Kurtz et al.²⁵ showed that in the air-sterilized polyethylene, *in vivo* oxidation was higher at the rim as compared to the dome of the TDR core and increased with implantation time. *In vivo* oxidation was correlated with the wear at the rim of the TDR, but not with the wear rates at the dome.

These three implant related failure mechanisms demonstrate that changes in fixation methods might achieve osteointegration to avoid migration, and that subsidence should be minimized by improving our insights in the consequences of bone quality and suboptimal matching of the TDR size or placement. To minimize wear debris, changes in packaging were performed. Furthermore, new promising technology, like highly cross linked polyethylene (HXLPE) stabilized by thermal treatments and by vitamin E, which have been developed to improve survival of THA and TKA, could also be applied to TDR to create a longer life span.

Implant failure may result in instability of the lumbar spine, which may cause for example hypertrophic bone formation and accelerated facet degeneration.²⁶ In a

biomechanical human cadaver study it was demonstrated that the flexion-extension range of motion and the segmental lordosis was significantly increased after TDR implantation in the lumbar spine, which could be explained by disruption of the longitudinal ligament and annulus during insertion of the TDR implant.²⁶ In our series, possibly due to instability of the TDR, some patients developed a scoliosis after TDR implantation (Figure 9.1). Future research is needed to study the effects of the TDR motion patterns on the load sharing at the implant level and on UHMWPE wear.²⁶ In addition, the risk of failure in multilevel TDRs is increased compared to single-level TDR.²⁷ Therefore we suggest that due to the broad unknown long-term success of TDR it should currently be considered carefully as a multi-level surgical treatment.

Figure 9.1 A) anteroposterior and B) lateral radiographs of a male patient developing a scoliosis after TDR implantation.

PROCEDURE REVISION SURGERY

In case of a failed TDR, revision surgery may be chosen as a treatment option. Important in choosing the appropriate strategy is characterizing the pain generator. In our series, the primary indication for revision surgery was recurrent or persistent back and/or leg pain. The cause of pain can be directly related to the implant, but also facet degeneration or adjacent segment degeneration may cause pain after TDR implantation.^{5,19,28-30}

In this thesis two surgical revision options were compared; namely *i)* removal of the TDR implant and filling the intervertebral disc with a graft combined with posterolateral instrumented fusion (“TDR removal group”) and *ii)* a posterolateral instrumented fusion without removal of the TDR implant (“fusion only group”). Both revision strategies aim to fuse the lumbar segments. Leaving the TDR *in situ* and performing a posterolateral instrumented fusion, would use the TDR as an anterior load-sharing device.

In our series we started with the posterolateral instrumented fusion to treat patients with a failed TDR who experienced recurrent or persistent low back pain. However, we learned from our own experience that a successful fusion alone gave unsatisfactory results, therefore we started to remove the TDR combined with fusion if the patient signed informed consent.

Removal surgery

In chapter 2, we described the technique and feasibility of TDR removal surgery in patients with a single or multi-level failed Charité TDR. The approach to remove a single-level L5-S1 TDR was in most patients similar to the implantation of a prosthesis,^{7,8} using an extension of the Pfannenstiehl incision. Using a lumbotomy, a TDR level L4-L5 or higher could be reached anterolaterally from the left side after mobilizing the m. psoas and exposing the lateral side of the disc level with the TDR. This way, mobilization of adherent great vessels in scar tissue could be avoided. If both L4-L5 and L5-S1 were retrieved, the lumbotomy was extended distally.

Intra-operatively, the most dangerous complications are vascular.³¹⁻³³ Most vascular injuries occur at the level L4-L5. At this level, the left common iliac vein and vena cava are most at risk since they are fragile and it may be difficult to manipulate them because of scar tissue from initial TDR implantation surgery. At L5-S1 the common left iliac vein is at risk.¹² In the TDR removal patient group, in 6 out of 21 patients (28.6%) a vascular injury was encountered. The availability of a vascular surgeon during TDR removal surgery is strongly recommended to immediately repair vascular complication and to avoid further complications because of potential retroperitoneal scarring. Damage to the major vessels may also occur directly from retractors inserted to obtain exposure of the disc, or from direct pressure if the duration of the surgery is too long (risk of deep venous thrombosis).⁷

Other potential complications are ureteral injury and damage of the neural prevertebral plexus, which in male patients can lead to retrograde ejaculation, loss of libido, or impotence.^{30,34} In all cases, the patient should be counseled about the potential risks and complications, which should be carefully weighed up against the possible benefits of revision surgery.

FINDINGS REVISION SURGERY

Clinical results

Although the mean Visual Analogue Scale (VAS) and Oswestry Disability Index (ODI) scores were not different between the TDR removal group and fusion only group, both revision procedures showed clinical improvement of $\geq 25\%$ in VAS and ODI scores at short- and mid-term follow-up (Table 9.1). These data showed that in the fusion only group a reduced number of patients experience improvement in VAS score of the posterolateral instrumented fusion surgery after mid-term follow-up (22%) compared to 1 year follow-up (50%). This is in agreement with our own experience, which taught us that a successful fusion only provides unsatisfactory results. Patients who underwent, as a second revision surgery, removal of the TDR, had a decreased VAS score ($P=0.06$)

Table 9.1 Percentage of patients demonstrating a clinical improvement of $\geq 25\%$ in VAS and ODI scores.

	VAS		ODI	
	1 year follow-up	Mid-term follow-up	1 year follow-up	Mid-term follow-up
Fusion only group	50%	22%	30%	27%
Removal group	43%	47%	30%	27%

Important in the clinical success between both revision strategies is that the patient should be counseled extensively about the risks and expectations. Patient expectations must be realistic in regard to the restricted degree of pain relief and possible complications of surgery. Furthermore, patients must also understand the limitations of our current knowledge regarding implant design and function, wear, tissue reaction to motion and degeneration of the operated and adjacent levels and other pain mechanisms.¹²

Tissue reactions

THA and TKA studies demonstrated the generation of UHMWPE wear debris from UHMWPE components in the tissues surrounding the hip or knee implant. These UHMWPE wear particles induce a periprosthetic inflammatory response.^{30,35} Submicron-sized particles tended to be the most bioactive. Phagocytosis of the UHMWPE particles, by macrophages and giant cells, leads to cellular activation and the release of proinflammatory cytokines, including interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF- α).³⁵ Although it was thought that UHMWPE wear would not be clinically relevant in TDR,³⁶ our data show the presence of micron-sized particles in all patients except one. The smaller particles were the most numerate, as seen in revision THA. In THA and TKA, submicron-sized particles appear to be critical in the phagocytosis. In TDR these

submicron UHMWPE particles were present. Despite similar size and shape of the submicron particles compared to THA, the lower concentration might explain the lower prevalence of osteolysis in TDR. In TDR both macrophages and giant cells were present, with relatively higher numbers of macrophages; however, the rates of macrophages in TDR were relatively lower than those in THA.

Besides the UHMWPE-on-metal TDR design, are metal-on-metal TDR designs available on the market. The proposed advantage of this alternative design is comparable to THA, namely the decreased particle-induced osteolysis. However, in a recent study submicron-sized metal particles were identified in macrophages in patients with a failed lumbar metal-on-metal TDR.³⁷ Analysis of the tissues collected during revision surgery revealed a likely delayed-type hypersensitivity-like reaction to the metal TDR. The tissue response was largely characterized by necrosis.³⁷

In addition to macrophages and giant cells, our findings showed that TNF- α and IL-6 are present in the periprosthetic tissue from TDR revision surgery.^{19,24,38} The presence of these inflammatory cells and cytokines suggests they play a role in TDR failure. We hypothesize that UHMWPE wear debris from TDR provokes an inflammatory response in periprosthetic tissue that is proportional to the volume of UHMWPE wear debris. Future studies will be necessary to provide more insight into the correlation between UHMWPE and metal wear debris and immune cells.

IMPLICATIONS FOR PUBLIC HEALTH

The knowledge on the clinical fate of the SB Charité III TDR has increased substantially since its introduction in regular patient care in 1989. Many changes have been made to optimize clinical results, like coated endplates, additional sizes and angles, and advanced sterilization processes. The challenges in creating a successful dynamic lumbar implant are enormous. A TDR aims to reduce pain while maintaining motion of the lumbar spine. The materials used for the implant should have a life-time durability. Next, a safe and effective surgical approach is necessary to enable the use of the implant on a large scale.

With the introduction of any new medical device like the TDR, it is important to know how to handle failures. Can the device, if necessary, be removed safely without major complications. If not, the use of such a medical device should be reconsidered.

In the present thesis we showed that in case of TDR failure, revision surgery as a treatment is feasible. We compared two surgical revision strategies. Both salvage strategies demonstrated clinical improvement at short and mid-term follow-up. The additional benefits of removing the TDR remains unclear. Therefore we suggest that, at present, posterolateral instrumented fusion alone will be sufficient in most cases. Alternative treatments, such as implantation of a new TDR or non-surgical treatment like pain-management, were not studied in the present thesis.

SUGGESTIONS FOR FUTURE RESEARCH

It is important to monitor the incidence of complications after TDR. Results from these studies give us important information about risk factors and they can be used for future clinical decision making. Furthermore, in patients who underwent removal of the TDR implant, periprosthetic tissue samples and the retrieved TDR core and metal endplates should be analyzed. The relationship between UHMWPE wear particles, inflammatory reactions, core damage and clinical improvement should be analyzed to provide insight into the success of these kind of devices. Extensive retrieval analysis research is necessary to establish the long-term performance and clinical significance of TDR implant wear, and to ultimately improve the next generation of TDRs. Based on these studies, TDR might become a better and safer treatment option with a life-long durability for patients with DDD.

TDR aims to relieve pain and to restore and maintain intervertebral segment motion while the adjacent levels are not overloaded. However, there is no consensus on this topic in literature. Continuous motion analysis should be performed to achieve insights in normal motion patterns in healthy persons and patients with a TDR implant. These TDR patients should undergo these analysis before TDR implantation and at different time-point postoperative to gather insights in motion patterns and changes in time.

Finally, prospective multi-center RCTs, preferably with long term follow-up, are crucial, including a full economic evaluation including all relevant costs when compared with clinical benefits, and with relevant control groups (e.g. fusion, conservative care programs) to establish cost-effectiveness and longevity of TDR. Issues that deserve particular attention are intra- and postoperative complications, risk factors for the development and progression of failed TDR, and treatment options of failed TDRs. We suggest that TDR surgery should only be performed within clinical trials until further documentation on its efficacy is provided.

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Summary

SUMMARY

Chapter 1 is the general introduction of this thesis, giving an overview of the development of the intervertebral disc prosthesis in the treatment of low back pain, and describing changes in the SB Charité III total disc replacement (TDR) design to improve the durability. From hip and knee arthroplasty revision surgeries it is known that ultra high molecular weight polyethylene (UHMWPE) wear debris may lead to failure of the prosthesis, necessitating revision surgery. This thesis encompasses two objectives. First, to study if TDR devices are safe and durable or if wear debris is of clinical concern; and secondly to study if there is an acceptable and safe procedure in case of TDR failure and if the device, if necessary, can be removed without major complications.

In **Chapter 2**, the surgical technique to remove a TDR and the occurrence of complications after TDR removal are described. The primary indication to remove the TDR was persistent or recurrent severe back pain. Additionally, the presence of a TDR related pathology like migration, subsidence, mal sizing, malposition and subluxation were observed on plain radiographs.

To remove a TDR, there are a couple of options with respect to approach and incision location. A lumbotomy from the lateral side was used to remove a single level L4-L5 (or higher) TDR. Level L5-S1 is addressed anteriorly with the same approach as the implantation of the TDR. When L4-L5 and L5-S1 were removed, an extended lumbotomy was performed. After TDR removal, the created defect was filled with a bone graft combined with a posterolateral instrumented fusion.

During revision surgery, the following complications were encountered: peroperative major vessel bleeding, a small colon lesion, and a lesion of the urether resulting in resection of the left kidney. Removal of the TDR was feasible, but it has its inherent risks because of nearby vascular structures and scar tissue.

Besides TDR removal combined with anterior lumbar interbody fusion followed by posterolateral instrumented fusion ("TDR removal group"), a posterolateral instrumented fusion without removal of the TDR implant ("fusion only group") was performed as another revision strategy in our outpatients clinic. Both revision strategies aim to fuse the lumbar segments. Leaving the TDR *in situ* and performing a posterolateral instrumented fusion, would use the TDR as an anterior load-sharing device. The experiences of both strategies after one year follow-up are described in **Chapter 3**. In the TDR removal group, the mean ($\pm$ sd) visual analogue scale (VAS) and oswestry disability index (ODI) decreased from 8.0 ($\pm$ 0.9) to 5.6 ($\pm$ 2.7) and from 56.3 ($\pm$ 14.0) to 43.0 ($\pm$ 20.7) respectively. Also an improvement in both scores were seen in the fusion only group, the VAS decreased from 8.0 ($\pm$ 0.9) to 6.3 ($\pm$ 2.1) and ODI from 57.0 ($\pm$ 17.0) to 44.6 ($\pm$ 20.4). According to the IDE-criteria, in which an improvement of $\geq 25\%$ in ODI was considered to be clinically improved, 30% in the fusion only group and 46% in the TDR removal group were clinically improved.

Chapter 4 compares the clinical mid-term results of both revision strategies in patients with a failed SB Charité III TDR after a mean follow-up of 3.7 year in the TDR removal group and 4.4 year in the fusion only group. The mean ($\pm$ sem) VAS decreases after revision surgery from 7.9 ($\pm$ 0.3) to 6.0 ($\pm$ 0.4) in the TDR removal group and from 7.8 ($\pm$ 0.2) to 7.0 ($\pm$ 0.4) in the fusion only group. The ODI in the TDR removal group improved from 54.8 ($\pm$ 2.8) to 47.9 ($\pm$ 3.8), and in the fusion only group from 57.3 ($\pm$ 3.9) to 48.2 ($\pm$ 4.6). Although the removal group showed a significantly lower VAS and ODI score post-revision surgery as compared to preoperatively, no significant differences were found between the removal and fusion groups before and after revision surgery in VAS and ODI score. A clinical relevant improvement of $\geq 25\%$ in VAS and ODI score was found in 47% and 21% respectively in the TDR removal group, and in 22% and 27% respectively in the fusion only group. However, the additional benefits of removing the TDR as compared to fusion alone at mid-term follow-up remains unclear. Therefore the clinical decision to remove the TDR should be carefully weighed up against the potential risks and complications of this procedure.

A frequently described complications after TDR is subsidence of the TDR implant into the bony endplate of the vertebrae. Subsidence may be the result of asymmetric implantation, undersizing of the implant or reduced bone quality. The importance of these factors is unknown, nor are objective methods available to quantify subsidence. In **Chapter 5**, a reliable method to measure the size of the TDR on both plain AP and lateral radiographs in relation to the size of the vertebral body and a method to measure and classify the presence of subsidence were designed using a custom developed software package implemented in Matlab. Subsidence was quantified by using thresholds for penetrated bone volume and rotation angles between TDR and bony endplate on level L4-L5, a penetrated bone volume $\geq 1300 \text{ mm}^3$ or a penetrated bone volume between $700\text{-}1300 \text{ mm}^3$ in combination with a rotation angle ≥ 7.5 degrees was defined as subsidence. High inter- and intra-observer correlation coefficients between three observers on two time-points indicate that a reliable method was designed to measure subsidence and ratio between the vertebral endplate and metal endplate of the TDR implant from AP and lateral radiographs. Furthermore, subsidence was shown to be related to undersizing of the TDR, a reduced risk of subsidence exists if more than 60% for L4 and 62% for L5 of the area of the bony endplate was covered by the TDR implant endplate.

The next three chapters of this thesis address research into tissue reactions that were observed after revision surgery.

In **Chapter 6**, periprosthetic fibrous tissue was analyzed using light microscopy with and without polarization filters. Ultra high molecular weight polyethylene (UHMWPE) wear particles $\geq 2.05 \text{ }\mu\text{m}$ were detected in the tissues from 15 of 16 patients. The smallest UHMWPE particles were the most numerate. Periprosthetic inflammatory reactions (lymphocytes, macrophages and giant cells) were present in 14 of 16 symptomatic TDR patients tissue. It is of clinical concern that UHMWPE wear and

inflammatory reactions are possible in the lumbar spine, because they may limit the longevity of TDRs in the lumbar spine.

Wear debris leading to particle disease, followed by osteolysis and aseptic loosening is often observed after total hip and knee arthroplasty (THA and TKA respectively). Although the presence of UHMWPE particles and periprosthetic inflammation after TDR has been demonstrated in the previous chapter, osteolysis is rarely observed in TDR patients. This **Chapter 7** compares the characteristics of UHMWPE wear particles and inflammatory reactions in periprosthetic tissue from revised TDR, THA and TKA components using light microscopy. Both small and large UHMWPE particles were present after TDR revision surgery and were comparable with both THA and TKA wear patterns. The broad range of length of these UHMWPE particles was comparable to TKA. Nevertheless, small round particles contained in macrophages were most numerous in TDR, due to domination of wear patterns similar to THA.

From THA and TKA it is known that submicron sized UHMWPE wear particles are the most bioactive. Therefore, **Chapter 8** described the results of scanning electron microscopy in a subgroup of our TDR cohort. The TDR revision tissues contained over a billion UHMWPE wear particles per gram between 0.05-2.00 μm length, and although significantly lower than THA tissue concentrations, this represents a substantial load within the spinal tissue. Moreover, despite 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 THA. These findings for historical gamma-irradiation-air sterilized UHMWPE implicate wear debris as an important factor contributing to the need for TDR revision surgery. The presence of UHMWPE particles of similar size and shape in TDR tissue, albeit lower in concentration, might explain why, unlike THA, pain rather than osteolysis is the major reason for revision surgery.

The general discussion in **Chapter 9** provides an overview and discussion about the main findings of the research presented in the previous chapters. The indications for revision surgery can be related to bone-implant fixation, bone failure around the TDR and wear debris. In case of a failed TDR, revision surgery may be chosen as a treatment option. Two surgical revision options were compared on per- and postoperative complications and clinical improvement. For future research it is important to monitor the incidence of complications after TDR and to analyze retrieved TDRs.

Samenvatting

SAMENVATTING

Hoofdstuk 1 geeft een overzicht van de ontwikkeling van de totale discusprothese (TDP) bij het behandelen van lage rugklachten. De SB Charité III discusprothese is de eerste discusprothese welke op grote schaal is toegepast in patiënten. Van knie- en heupprothesen is bekend dat polyethyleen (ultra high molecular weight polyethyleen, UHMWPE) slijtage deeltjes kunnen leiden tot het falen van de prothese, waardoor een revisie operatie vereist is. Het doel van dit proefschrift is tweeledig. Enerzijds het bestuderen of discusprothesen veilig en duurzaam zijn en/of slijtage deeltjes klinisch relevant zijn. Anderzijds, of in het geval dat een discusprothese faalt, het mogelijk is om deze patiënten operatief te behandelen.

In **hoofdstuk 2** wordt de operatietechniek voor het verwijderen van een SB Charité III discusprothese beschreven, en de complicaties die hierbij optraden. De primaire indicatie voor het verwijderen van een discusprothese was aanhoudende of nieuw ontstane rugpijnklachten. Daarnaast werden op röntgenfoto's de volgende afwijkingen gevonden: migratie van de prothese, verzakking van de prothese in het wervellichaam (subsidence), verkeerde maat en/of plaatsing van de prothese en subluxatie.

Afhankelijk van het niveau van de prothese wordt voor het verwijderen van de discusprothese een chirurgische benadering gekozen. Een laterale lumbotomie wordt toegepast bij een discusprothese op het niveau L4-L5 (en daarboven), terwijl het niveau L5-S1 anterieur word benaderd. Indien zowel een discusprothese op niveau L4-L5 als L5-S1 werd verwijderd, werd een uitgebreide lumbotomie toegepast. Na het verwijderen van de discusprothese werd de ontstane holte opgevuld met een bot transplantaat en werd een posterolaterale geïstrumenteerde fusie uitgevoerd.

In onze patiënten traden tijdens het verwijderen van de discusprothese vasculaire complicaties op, een laesie van de dikke darm en een laesie van de ureter waarbij uiteindelijk de linker nier verwijderd moest worden. Het verwijderen van de discusprothese was mogelijk, maar het neemt wel risico's op complicaties met zich mee als gevolg van de nabijgelegen vaten en het littekenweefsel.

In onze kliniek is naast het verwijderen van de discusprothese gevolgd door een posterolaterale geïstrumenteerde fusie ("TDP verwijder groep"), een posterieure geïstrumenteerde fusie zonder het verwijderen van de discusprothese ("fusie alleen groep") uitgevoerd als tweede revisie operatietechniek. Beide revisie technieken hebben als doel het fuseren van de lumbale wervels. In het geval dat de discusprothese *in situ* blijft, wordt deze prothese als een anterieur 'load-sharing device' gebruikt. De 1 jaars follow-up resultaten van beide revisie technieken worden beschreven in **hoofdstuk 3**. In de TDP verwijder groep daalde de gemiddelde ($\pm$ sd) visueel analoge schaal (VAS) van 8.0 ($\pm$ 0.9) naar 6.5 ($\pm$ 2.7) en de oswestry disability index (ODI) van 56.3 ($\pm$ 14.0) naar 43.0 ($\pm$ 20.7). In de fusie alleen groep zijn beide scores ook gedaald, namelijk de VAS van 8.0 ($\pm$ 0.9) naar 6.3 ($\pm$ 2.1) en de ODI van 57.0 ($\pm$ 17.0) naar 44.6 ($\pm$ 20.4). Een toename van 25% of meer in de ODI score wordt

beschouwd als klinisch relevant verschil. In de fusie alleen groep is in 30% van de patiënten en in de TDP verwijdering groep is in 46% van de patiënten een klinisch relevante verbetering opgetreden 1 jaar na de revisie operatie.

Hoofdstuk 4 vergelijkt wederom de resultaten van beide revisie technieken maar nu met een follow-up van 3.7 jaar in de TDP verwijder groep en 4.4 jaar in de fusie alleen groep. De gemiddelde VAS ($\pm$ sem) daalde na revisie operatie van 7.9 ($\pm$ 0.3) naar 6.0 ($\pm$ 0.4) in de TDP verwijdergroep en van 7.8 ($\pm$ 0.2) naar 7.0 ($\pm$ 0.4) in de fusie alleen groep. De ODI verbeterde in de TDP verwijdergroep van 54.8 ($\pm$ 2.8) naar 47.9 ($\pm$ 3.8) en in de fusie alleen groep van 57.3 ($\pm$ 3.9) naar 48.2 ($\pm$ 4.6). Er zijn geen significante verschillen gevonden tussen de twee revisie technieken op beide tijdstippen. Een klinisch relevante verbetering van tenminste 25% in VAS en ODI scores zijn respectievelijk gevonden in 47% en 21% van de patiënten in de TDP verwijder groep en in 22% en 27% van de patiënten in de fusie alleen groep. Echter, de voordelen van het verwijderen van de discusprothese in vergelijking tot het *in situ* laten van de discusprothese zijn op middellange termijn nog niet duidelijk. De keuze voor het wel of niet verwijderen van de discusprothese dient tegen de potentiële risico's en complicaties afgewogen te worden.

Een vaak omschreven complicatie die ontstaat bij patiënten met een discusprothese is het inzakken van de prothese in de benige eindplaat van de wervel, ook wel "subsidence" genoemd. Subsidence kan veroorzaakt worden door asymmetrische implantatie, te kleine maat van de TDP of verminderde botkwaliteit. In **hoofdstuk 5** wordt een betrouwbare methode beschreven om de grootte van de discusprothese te meten op zowel anteroposterieure (AP) en laterale röntgenfoto's in verhouding tot de grootte van het wervellichaam, en een methode voor het meten en classificeren van de aanwezigheid van subsidence. Subsidence is gekwantificeerd met behulp van drempelwaarden voor botvolume verlies en rotatiehoeken tussen de discusprothese en benige eindplaat op het niveau L4-L5. Een botvolume verlies van $\geq 1300 \text{ mm}^3$ of een botvolume verlies tussen 700-1300 mm^3 in combinatie met een rotatiehoek van ≥ 7.5 graden werd gedefinieerd als het hebben van subsidence. Hoge inter- en intra-beoordelaars correlatiecoëfficiënten van drie beoordelaars op twee tijdstippen laten zien dat een betrouwbare methode is ontwikkeld om subsidence te meten en de verhouding tussen de benige eindplaat van de wervel en de metalen eindplaat van de TDP op basis van AP en laterale röntgenfoto's. Bovendien tonen de resultaten aan dat het ontstaan van subsidence gerelateerd is aan de grootte van de discusprothese. Er is een verminderde kans op subsidence als meer dan 60% voor L4 en 62% voor L5 van de benige eindplaat wordt bedekt door de metalen eindplaat van de discusprothese.

De volgende drie hoofdstukken van deze thesis gaan in op lichaamsvreemde weefselreacties die optreden na een revisie operatie.

In **hoofdstuk 6** wordt periprosthetisch fibreus weefsel geanalyseerd met behulp van een lichtmicroscop met en zonder polarisatie filters. Polyethyleen (UHMWPE) slijtage deeltjes $\geq 2.05 \text{ }\mu\text{m}$ werden gedetecteerd in het weefsel van 15 van de 16 patiënten. De kleinste UHMWPE slijtage deeltjes kwamen het meest frequent voor. Daarnaast

waren ontstekingsreacties (lymfocyten, macrofagen en/of reuscellen) aanwezig in het weefsel van 14 van de 16 discusprothese patiënten. Dit hoofdstuk toont aan dat UHMWPE slijtage deeltjes en ontstekingsreacties aanwezig kunnen zijn in de lumbale wervelkolom na implantatie van een discusprothese, welke mogelijk de levensduur van de discusprothese in de lumbale wervelkolom beperken.

Uit de literatuur is bekend dat deze UHMWPE slijtage deeltjes na een totale heup- en knieprothese (THP en TKP respectievelijk) kunnen leiden tot “particle disease”, met osteolyse en aseptische loslating tot gevolg. Hoewel de aanwezigheid van UHMWPE slijtage deeltjes en periprosthetische ontstekingsreacties na implantatie van een discusprothese is aangetoond in het vorige hoofdstuk, word osteolyse zelden bij discusprothese patiënten waargenomen. **Hoofdstuk 7** vergelijkt de eigenschappen van UHMWPE slijtage deeltjes en ontstekingsreacties in periprosthetisch weefsel van gereviseerde TDP, THP en TKP patiënten. De brede range van de lengte van de TDP UHMWPE slijtage deeltjes was vergelijkbaar met TKP slijtage deeltjes. Echter, de kleine ronde deeltjes waren het meest talrijk in de discusprothese groep, hetgeen vergelijkbaar is met THP slijtage patronen.

Van THP en TKP is bekend dat submicron UHMWPE slijtage deeltjes het meest bio-actief zijn. **Hoofdstuk 8** beschrijft de resultaten van scanning elektronen microscopie, welke in een subgroep van ons discusprothese cohort is uitgevoerd. Het discusprothese weefsel, dat tijdens de revisie operatie is verzameld, bevat meer dan één miljard UHMWPE slijtage deeltjes per gram weefsel met een lengte tussen de 0.05-2.00 micrometer. Ondanks dat de concentratie lager was dan in THP weefsel, betekent dit wel dat er een aanzienlijke belasting is in het spinale weefsel. Echter, ondanks de verschillen in load en kinematica tussen de lumbale wervelkolom en de heup, zijn de grootte en de vorm van de slijtage deeltjes vergelijkbaar tussen deze twee groepen. Deze resultaten impliceren dat de aanwezigheid van slijtage deeltjes een belangrijke factor is die bijdraagt tot de noodzaak voor het uitvoeren van een discusprothese revisie operatie. De lagere concentratie van UHMWPE slijtage deeltjes van vergelijkbare grootte en vorm in het fibreuze weefsel in de discusprothese-groep in vergelijking met THP, zou kunnen verklaren waarom, in tegenstelling tot de THP, pijn in plaats van osteolyse de belangrijkste reden voor revisie chirurgie is.

De algemene discussie in **hoofdstuk 9** geeft een overzicht van de belangrijkste resultaten van het onderzoek uit de voorgaande hoofdstukken. De indicaties voor revisie chirurgie kunnen gerelateerd zijn aan bot-implantaat fixatie, het falen van het bot rond de discusprothese en slijtage deeltjes. In geval van het falen van een lumbale discusprothese, kan revisie chirurgie als behandel strategie worden overwogen. Twee revisie technieken zijn onderling vergeleken op het ontstaan van complicaties en klinische verbetering van de patiënt. Voor toekomstig onderzoek is het belangrijk om de incidentie van complicaties na een discusprothese te monitoren en om gereviseerde prothesen te analyseren.