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Increased risk for periprosthetic joint infection in male patients – an analysis of 335 revision total joint arthroplasty cases

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Abstract

Total joint arthroplasty is a highly successful surgical procedure, immensely increasing the quality of life of patients who suffer from chronic degenerative joint diseases. In future generations of younger and more active patients the number of primary total joint arthroplasties is going to continue to rise. Concomitant with that, the number of revision total joint arthroplasties will also rise. These revision arthroplasties are more challenging and more threatening to the patients' health than primary arthroplasties. This single-institutional analysis of 335 revision total joint arthroplasty cases performed during the years 2011 and 2016 at the department for orthopaedic surgery of the University hospital Magdeburg revealed not only that there is a difference in the reasons for revision between the male and female sex but also a striking correlation between the male sex and the incidence of periprosthetic joint infections. Also, a risk factor analysis for some of the most common risk factors for the incidence of periprosthetic joint infections exposed a more than six times higher risk for the incidence of periprosthetic joint infections in patients who already underwent a revision surgery. The data also revealed a more than three times higher risk of periprosthetic joint infections in the male sex when compared to the female sex. These results should be considered during the treatment of patients with primary and revision total joint arthroplasties. Not only, but especially male patients with complications of a total joint arthroplasty require a thoroughly performed diagnostical process to detect periprosthetic joint infections in an early state.

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Abbreviations

TJA	total joint arthroplasty
THA	total hip arthroplasty
TKA	total knee arthroplasty
OA	osteoarthritis
RA	rheumatoid arthritis
WHO	World Health Organisation
CT	computed tomography
MRI	magnetic resonance imaging
PFF	proximal femur fracture
FHN	femoral head necrosis
ARCO	Association de Recherche de la Circulation Osseouse
CoCrMo	cobalt-chromium-molybdenum
PE	polyethylene
UHMWPE	ultra-high molecular weight polyethylene
XPE	crosslinked polyethylene
Cer	ceramics
Ti	titanium
MoM	metal on metal
MoP	metal on polyethylene
CoP	ceramics on polyethylene
CoC	ceramics on ceramics
PMMA	polymethylmetacrylate
PJI	periprosthetic joint infection
QoL	quality of life
e.g.	for example
BCIS	bone cement implantation syndrome
rTJA	revision total joint arthroplasty
ARMD	adverse reaction to metal debris
CRP	C-reactive protein

1. Introduction

Total joint arthroplasty (TJA) is a very successful surgery and therefore has been defined as “the operation of the century” (Learmonth et al. 2007). TJA has become a fundamental part of modern orthopaedic surgery with a huge benefit for patients, who suffer from chronic degenerative joint diseases. With a successful TJA, the improvement in the patients quality of life is immense (Liebs et al. 2016). Due to the demographic changes in society, TJA rates are expected to drastically increase within the next years. However, an increased implantation rate is also accompanied by an increase in revision cases. Revision surgeries are a greater burden for the patient as well as the health-care system, compared to primary implantations (Kurtz et al. 2012). The following chapters of this thesis aim to provide a theoretical background to primary and revision total joint arthroplasty as well as characteristics and potential risk factors leading to the failure of TJA.

1.1 Total Joint Arthroplasty

Total Joint Arthroplasty is a form of a surgical procedure, where a dysfunctional or arthritic joint is replaced with a device, called an endoprosthesis. The endoprosthesis is designed to imitate the function and movement of a native joint. The main causes for dysfunctional joints are chronic degenerative joint diseases, congenital disorders or, especially concerning the hip joint, bone fractures that occur most often in patients with pre-existing pathologies such as osteoporosis or malignant diseases. TJA is considered when less invasive or conservative treatment methods have failed. The most common patient sites for TJA are the hip and the knee joint, but there are also surgical techniques to replace the shoulder, finger, vertebra or ankle joint. Already in an early post-operative state, the gain of function and mobility is significant, markedly increasing the patient’s quality of life (QoL) (Mandzuk et al. 2015). TJA is an intervention that needs to be adapted to the patient’s individual characteristics (incl. anatomy, sensitivities). Especially in a generation with younger and more active patients receiving TJA, the demands on TJA are increasing. Over the past decades a huge variety of total joint arthroplasties has derived from research, with different surgical techniques, different materials, different fixation

methods and different postoperative treatment concepts. In the following chapters these achievements will be discussed in more detail.

1.1.1 Indications

This chapter is going to portray the most common indications for TJA. As reported by the Swedish national hip joint replacement register for total hip arthroplasty (THA) the most common indications are osteoarthritis (80.8%), hip fracture (8.7%) and femoral head necrosis (2.3%). According to the national joint registry for England, Wales, Northern Ireland and the Isle of man for total knee arthroplasty (TKA) the most common indication is osteoarthritis (97.3%) (Kärrholm et al. 2017) (National Joint Registry 2018).

1.1.1.1 Osteoarthritis

Osteoarthritis (OA) is a chronic degenerative joint disease and on a global scale the most common joint disease. It is defined by the American College of Rheumatology as a group of conditions that lead to joint signs that are associated with abnormal integrity of articular cartilage and related changes in the underlying bone (Altman et al. 1986). The loss of cartilage, remodelling of the underlying bone and local inflammation lead to a clinical syndrome of joint pain, loss of function and reduced QoL. Even though there is a repairing mechanism in the affected joints, recovery is only temporary and the disease is progressive. (National Clinical Guideline Centre (UK) 2014).

The original idea, that OA is a degenerative joint disease secondary to aging has long been reconsidered. It has a multifactorial genesis including inflammation, cellular processes, genetics, mechanical stress and joint integrity (Kahn, Xu 2017). In the most common form of OA, the primary or idiopathic form, a clear predisposing pathology is missing. The secondary form of OA can result from trauma, endocrine disorders, congenital disorders, metabolic disbalances, septic diseases or circulatory disorders (Günther et al. 2013). There are certain risk factors for the development of OA, including the patients age and sex, obesity and physical inactivity, osteoporosis or occupations involving repetitive, physical labour (Sarzi-Puttini et al. 2005).

According to the GEDA 2014/2015 study of the Robert-Koch-Institute, 17.9 % of the German population older than the age of 18, were diagnosed with OA. There has been an increase in the incidence of OA when the year 2000 is compared to the year 2016. The incidence of OA is higher in the female

population with a percentage of 21.8% compared to the male population with a percentage of 13.9% (Fuchs et al. 2017).

There are conservative and operative treatment options for OA. TJA as a joint replacing technique is currently a recommended and the most effective treatment for patients with end-stage OA. It increases the patient's QoL significantly compared to the preoperative condition (Liebs et al. 2016).

1.1.1.2 Proximal femur fracture

Proximal femur fractures (PFF) can be categorised as either subtrochanteric, trochanteric or femoral neck fractures. Possible pathomechanisms include a stumble and fall on the hip in older patients and high-speed trauma predominantly in younger patients. PFF are associated with increased age and incidence of osteoporosis. According to a study of Kanis et al., on a global scale Germany belongs to the countries where patients have a high risk for the development of PFF (Kanis et al. 2012). With a mortality rate of 5.5 / 100 000, PFF had the highest mortality rate in the category of all fractures in the year 2016 (Robert-Koch-Institut 2016).

Because of poor results, conservative treatment methods should be an exception for patients who refuse to get surgery or patients with comorbidities that make an operative treatment impossible. Operative treatment methods can be either joint preserving or joint replacing. Joint replacing treatment aims at quickly improving mobility and helping with an early integration in the patient's daily routine (Klopfer et al. 2017).

1.1.1.3 Femoral head necrosis

Osteonecrosis is usually an aseptic, ischemic necrosis mainly in the epiphysis, the resulting loss of function of the affected joint is critical. The femoral head is the most common site for aseptic osteonecrosis. If progressive and without treatment, femoral head necrosis (FHN) leads to the secondary form of OA (Kramer et al. 2000). There are many potential causative factors related to the incidence and progression of FHN. The main non-traumatic causes are systemic steroid administration, alcohol abuse or idiopathic occurrence (Wang et al. 2013c). The causative factors lead to a disturbance of microcirculation in the femoral head, eventually ending in ischemia and bone necrosis. The annual incidence is estimated to be 0.01% in German speaking countries. The incidence of FHN is 4 times higher in

male patients when compared to female patients. The mean age of incidence is at 35 years (Hofmann et al. 2005). In early stages of FHN, the therapy aims at reducing the mechanical load on the hip joint, to then allow blood recirculation in the femoral head (Mont, Hungerford 2000). If conservative or joint-preserving treatment methods fail, THA is indicated (Deutsche Gesellschaft für Orthopädie und Orthopädische Chirurgie 2014).

In conclusion, the previous chapter described the most common indications for TJA, osteoarthritis, proximal femur fracture and femoral head necrosis. Their incidence has been increasing over the last couple of years. With a high prevalence of risk factors for the development of those diseases, consequently the demand for sufficient treatment options has also been increasing. Various alternative treatment options have been developed, but in most cases TJA is indicated. The following chapter will focus on how the evolution of TJA meets the increasing demands.

1.1.2 Progress in research on total joint arthroplasty

Total joint arthroplasty is a very successful procedure. It aims to relieve pain, increase joint stability and correct deformities. During the past decades scientists and surgeons have created and improved many different types of TJA. Over the last years, the demands for TJA have increased drastically. In the current generation younger patients are affected, who live longer and who tend to place more strain on implants via higher activity levels. TJA are needed, that provide good long-term survival rates. The various premises for a successful TJA include an ideal implant design, materials with good biomechanical properties and biocompatibility as well as optimal fixation techniques, improved instrumentation and easier revision surgery. The following chapter is going to give a brief overview of the progress in TJA research over the past decades, focusing on the demands and challenges, that past and modern TJA had to face.

1.1.2.1 History of TJA

In 400 BC, Hippocrates of Kos is said to be the first who concerned himself with congenital hip disorders and discerned missing treatment methods. But it took another 2200 years until the first operative treatment of a disordered hip was performed by R. Barton, an American orthopaedic surgeon, in 1797

(Barton 1827). Due to adverse reactions, the preferred materials for TJA have changed from organic materials such as the patient's skin, muscle tissue, joint parts of corpses or ivory, used e.g. by Gluck, a German orthopaedic surgeon, to non-organic, less immuno-allergotoxic materials, such as wood, glass or metal (Hernigou 2013)(Reimers 1970). In the year 1938 the first biomedical metal alloy, a Cobalt-Chromium-Molybdenum alloy (CoCrMo-alloy), also called vitallium, was introduced (Hernigou 2014). Soon CoCrMo-alloys became the leading material for endoprosthesis. Starting from the year 1953, the use of metal on metal (MoM) total hip arthroplasty became popular (Knight et al. 2011). The idea of hemiarthroplasty came up and led to the development of models for the hip and knee joint (MacIntosh, Hunter 1972).

Up until 1959 there was an absence of sufficient fastening material. But with the discovery of Polymethylmethacrylate (PMMA) as bone cement by Sir John Charnley, a British orthopaedic surgeon, the implantation of artificial joints was popularised. Charnley`s low friction hip joint replacement device, where polyethylene as a soft bearing partner and metal alloys as a hard bearing partner articulate, was so successful that he is now considered the father of modern THA (Charnley 1970b). Due to a higher quantity of failing cemented endoprosthesis, advances in the design of endoprosthesis to offer a sufficient cementless fixation were accomplished (Mittelmeier 1974).

With the two fixation techniques (cemented vs. cementless) been implemented, the next goal of researchers was to design an artificial joint that matched the biomechanical demands of the human joint and that offered a high biocompatibility as well. During the following 40 years in the history of TJA, different materials, some of which are still in use today, were introduced and modified, including titanium-based alloys (Ti), ceramics (Cer) and polyethylene (PE). As a result of about 200 years of research, many options of implantation- and fixation techniques as well as design and material choices were developed and a huge variety of endoprosthesis was generated. Some of them were proven to cause great harm to the patient's health like MoM bearings (see chapter 1.2.2 Reasons for revision). Others are lacking sufficient research to determine long-term survivorship and negative consequences for the human body. But those providing excellent

results regarding biocompatibility and mechanical properties are established in modern orthopaedic surgery.

1.1.2.2 Past and modern bearing materials

Considering the potential health-related risks deriving from metal debris in MoM joint arthroplasties, it is mandatory to design and establish TJA with bearing materials, that do not only meet the mechanical requirements of the natural joint but also show a high biocompatibility with reduced or absence of adverse reactions. The implantation of strange materials in the human body is restrained by a foreign body reaction. This is an inflammatory response that may lead to migration and rejection of the implanted material. Therefore, any material applied into the human body should show a high degree of biocompatibility and also have the ability to perform with an appropriate host response (Williams 1999). Some of the expectations from updated bearing materials are increased hardness to decrease the risk of breaking or scratching, increased wear resistance, low friction behaviour and allowance of implantation of larger implant components to minimize dislocation rates. The materials discussed in this chapter were chosen because they currently are the most frequently used materials in TJA. The following chapter aims at depicting the advantages and disadvantages of each bearing material and at providing a short overview of the current stage of research as well as possible future bearing materials. Emphasis will be put on bearing materials in THA, since in TKA polyethylene inlays are the present gold standard. Possible current bearing material combinations are hard-on-soft couples, including metal on polyethylene (MoP) and ceramics on polyethylene (CoP), and hard-on-hard couples, including MoM and ceramics on ceramics (CoC).

<u>Metal bearings</u>

Soon after the introduction of biomedical metal alloys they became the leading trend for research in the design of endoprostheses. Metal alloys as material for bearings were expected to allow a better range of motion while providing higher stability and scratch resistance due to their hard surface material. Archard stated that volumetric wear is inversely proportional to the hardness of the softest bearing material, metal alloys therefore would be fitting bearing materials (Archard 1953). In 1951, the first MoM hip arthroplasty, made from stainless steel was implanted. However, it failed

shortly after implantation because metal debris occurred (McKee 1951). Sir John Charnley stated that a MoM bearing will most certainly produce a substantial amount of metallic debris over a period from 15 or 20 years (Charnley 1970b). Following that, during the 1970`s due to metallic debris and theoretical carcinogenic risks, MoM bearings were disregarded (Deutman et al. 1977). But 30 years later, when the potential complications of polyethylene wear in young total hip arthroplasty patients were investigated, MoM implants gained popularity again, due to their advanced mechanical properties. In particular, larger femoral head sizes in MoM implants have been used frequently in cases with instability risk factors, to achieve greater component stability and lower rates of dislocation (Cho et al. 2016). That led to a rising popularity of MoM hip bearings over the last decades. When studies revealed that metal debris does occur in MoM TJA and it does lead to higher blood ion levels of cobalt or chromium and adverse reactions (ARMD) again the focus was put on alternative bearing materials (MacDonald et al. 2003) (Bolland et al. 2011). Additionally, poorly performing devices were withdrawn from the market and the opinion, that MoM total joint arthroplasties should no longer be performed was derived from that expertise. (Therapeutic Goods Administration 2011).

Polyethylene bearings

Initial unsuccessful experiments with polymers as a bearing material eventually led to the development of ultra-high molecular weight polyethylene (UHMWPE), which was incorporated in John Charnley`s idea of a low friction arthroplasty (Charnley 1970b). Soon UHMWPE became the preferred bearing material because of its good wear resistance. But as studies reported higher levels of wear debris that lead to osteolysis and aseptic loosening in THA with polyethylene as a bearing material research had to be done to improve the quality of UHMWPE bearings so it would keep up with alternative materials. The solution was the development of cross-linked PE (XPE), which is UHMWPE modified by using gamma radiation and thermal treatment. It proved to have a good tribological performance and a lower wear rate compared to UHMWPE. Until today it remains the preferred bearing material in THA (Galvin et al. 2010) (Ayers et al. 2015). The negative co-effects of gamma irradiation, oxidation products and free radicals that damage the XPE, can be avoided by adding the antioxidant vitamin E. In simulator

studies by Micheli et al. Vitamin E-doped XPE showed promising results, but long-term studies are required to confirm its effectiveness (Micheli et al. 2012). In TKA, XPE is the current standard as an interface.

Ceramic bearings

Concerns regarding the problem of PE wear debris associated osteolysis in soft bearings and adverse reactions in MoM bearings led to the introduction of ceramic-on-polythylene (CoP) and ceramic-on-ceramic bearings (CoC). Ceramics are harder than metals, biologically inert and have good lubrication properties, which is essential for reduced friction. They provide excellent durability and good long-term results (Unsworth 2012). Several studies indicate little to no osteolysis in CoC bearings, proving their function in minimizing wear-related osteolysis. (Lusty et al. 2007) (Yoo et al. 2005). Problems of CoC bearings were squeaking and breaking of the implant, especially in early-generation ceramics (Ha et al. 2007). Squeaking, as a potential indication for revision surgery, is a phenomenon that occurs in TJA with hard-on-hard bearings, with a greater incidence and persistence in CoC bearings than in MoM TJA (Walter et al. 2010) (Jarrett et al. 2009). Squeaking occurs due to vibrations caused by friction acting of the artificial joint components. A study by Hothan et al. revealed, that the occurrence of squeaking and the squeaking frequency is determined by the design of the artificial joint components and mainly influenced by the stem design (Hothan et al. 2011). Concerning the breaking of ceramic implants, recent reports by the Australian Orthopaedic Association National Joint Registry showed a low risk of ceramic fracture in the new-generation of mixed ceramics. (Australian Orthopedic Association 2014). The use of CoP THA is gradually gaining popularity, though it is still not very widely used. Clinical and simulator data have shown that wear rates for CoP bearings are significantly lower than in MoP bearings (Clarke, Gustafson 2000) (Semlitsch, Willert 1997). An attempt to reduce not only the metal wear debris and local tissue reactions but also the squeaking and implant breaking of ceramic components is the combination of both: a ceramic-on-metal (CoM) arthroplasty. Simulator studies showed promising results, but in vivo studies revealed contradicting results and Schouten et. al. showed, that there is an equivalent increase in blood metal ion levels when CoM and MoM bearings were compared (Schouten et al. 2017).

1.1.2.3 Fixation methods

To maintain long-term survivorship of TJA, not only the material quality is important but also a sufficient fixation of the artificial joint parts is needed. Currently there are the options of cemented or uncemented fixation. Both techniques' history as well as their advantages and disadvantages will be explained in the following chapter.

Cemented fixation

The history of cemented endoprosthesis begins with John Charnley, who used acrylic bone cement to bond femoral head prosthesis into the femur in 1958. Back then, the cement components were mixed with a spatula in a bowl and the surgeon would knead the cement mass and manually insert it into place. Early cementing techniques showed promising survival rates (Charnley 1970a). Findings from post-mortem studies and in vitro tests with bone cement led to the development of second- and third-generation cementing techniques, where prosthesis positioning devices and porosity reducing measures were used for correct placement of the prosthesis and a reliable thickness of the cement mantle could be achieved. These improved techniques led to an increased survival rate of up to 90% after 15 years follow-up (The Norwegian Arthroplasty Register 2003) (Benjamin et al. 1987). Cemented fixation may offer an immediate strong connection between bone and implant that allows an early weight bearing, but a meta-analysis by Yoon et al. showed that cemented fixation is associated with higher rates of periprosthetic joint infection (Yoon et al. 2015). In addition to that, there are disadvantages in cemented TJA that lead to a higher vulnerability of the bone. These circumstances include the possibility of bone necrosis due to the exothermic reaction during the polymerization of the bone cement (Mjöberg et al. 1984). Another disadvantage of cemented TJA are cardiopulmonary complications, also considered as bone cement implantation syndrome (BCIS). BCIS is characterized by clinical features that are threatening to the patient`s health and may include hypoxia, hypotension, cardiac arrhythmias and cardiac arrest (Parvizi et al. 1999) (Modig et al. 1975). Because of the higher infection rate in cemented TJA, the use of antibiotic-impregnated bone cement is recommended. A meta-analysis by Wang et al. revealed, that the prophylactic use of antibiotic-impregnated

bone cement reduces the risk for infection in primary TJA (Wang et al. 2013a).

Uncemented fixation

Since the 1970s uncemented fixation, using porous surfaces and osteoconductive coatings, has become available. Uncemented fixation has the advantage of shorter operation times and easier revision surgery. A disadvantage is the weaker fixation into the bone. In TJA, cemented arthroplasty provides immediate fixation, while in uncemented arthroplasty bone in-growth needs to happen before it is considered well fixed. For the decision, if cemented or uncemented fixation is applied, patient characteristics, like bone density for example, should also be considered. A study by Drexler et al. shows, that for TKA there are similar results when cemented and uncemented prosthesis are compared, due to the higher possibility of revision surgery, uncemented TJA is suggested in younger, more active patients (Drexler et al. 2012). For THA, studies based on national joint registers from Sweden and a combined register of the Nordic nations show inferior long-term survival rates of uncemented compared to cemented THA, with an increased risk of revision in uncemented THA (Hailer et al. 2010) (Mäkelä et al. 2014). The cemented femoral components provide immediate post-operative stability with better integration between bone, cement, and prosthesis, leading to earlier pain relief and weight bearing. A study by Unnanuntana et al. also shows, that the costs for the implantation of cemented prostheses are lower than for cementless prostheses (Unnanuntana et al. 2009). The implantation of a cemented endoprosthesis therefore remains an attractive fixation method, despite the increasing demand for uncemented endoprosthesis.

1.1.2.4 Future bearing materials

Despite the availability of adequate materials with good long-term results and a good biocompatibility the research for alternative, better materials is still ongoing. This chapter aims at giving a brief overview of some of the future bearing materials. It is to be noted, that the list of these further mentioned material options is by no means complete. For most of the following material options there is not enough clinical evidence yet for them to be established in modern orthopaedic practices.

There are various options for changing material properties in an artificial joint. One of them is to replace or refine the bearing materials. Non-oxide ceramics for example, also used for space technology, are suitable for TJA because of their increased ductility and resistance to higher loads. (Mazzocchi, Bellosi 2008). Little has been published about non-oxide ceramics in TJA and a controversial discussion is taking place about the development of an increased third-body wear, which is wear related osteolysis due to particles between softer articulating surfaces, in TJA with non-oxide ceramics (Rahaman et al. 2007). Another example for modifying the bearing materials are cushion bearings. They attempt to mimic the natural joint`s tribology. Just like natural cartilage, this concept aims at minimizing the mechanical load that is lasting on the artificial joint parts and the underlying bone. Polyurethane as an example for cushion bearing surfaces offers a possible fluid-film lubrication with promising tribological properties and shows better ageing resistance than PE (Kurtz et al. 2010).

A different approach to perfecting bearing materials that is currently investigated is the addition of multiwalled carbon nanotubes into PE. This method aims at increasing toughness of PE. Ruan et al. were able to prove that nanotube-reinforced PE has an increase in strength, ductility and strain energy density when compared to UHMWPE (Ruan et al. 2003).

Instead of changing the bearing material, applying a coating to the surface of established bearing materials can also lead to different tribological properties. For example, coatings with diamond-like carbon show low wear rates against PE compared with conventional materials without coating in simulator tests for the hip and knee joint (Affatato et al. 2000) (Oñate et al. 2001). However, in vivo tests point out the problem of inadequate adhesion of the coating which eventually chips off and leads to higher revision rates when compared to conventional CoP bearings due to third-body wear (Taeger et al. 2003).

Surface modifications as another option for future bearing materials, in contrast to coating, chemically transform the outer layers of bearing materials, thus lowering the risk for third-body wear. Surface oxidized zirconium for example offers an increased hardness and wettability that lead to fluid-film lubrication and decreased wear rates against PE when compared with CoCrMo in simulator studies (Good et al. 2003)(Ezzet et al. 2004). To

reveal the potential and possible negative effects of surface modifications long-term studies need to be done.

In conclusion, due to substantial advances in the research for bearing materials with good tribological properties and a high biocompatibility, sufficient fastening materials and operation techniques, TJA has become a successful surgery. It meets the requirements to be an adequate response to the rising incidence of chronic degenerative joint diseases in our generation. The increasing number of primary TJA performed annually is accompanied by an inevitable increase in revision TJA. The reasons for as well as the problems of revision surgery will be outlined in the next chapter.

1.2 Revision Total Joint Arthroplasty

1.2.1 Definition

Revision total joint arthroplasty (rTJA) means that a joint arthroplasty-operated patient undergoes a further operation, in which a part or the whole prosthesis is replaced or extracted. A revision operation is economically and technically more demanding and requires a more extensive use of resources than a primary TJA.

1.2.2 Reasons for revision

The complications of TJA can be divided into three groups: intra-operative, early and late post-operative complications. In this chapter, mainly the late-postoperative complications are portrayed because they are the main reasons for revision surgery in TJA. For the sake of completeness however, intra-operative and early postoperative complications are paraphrased. The intraoperative complications can include lesions of blood vessels or nerve fibres, fracturing of bones, mispositioning of the endoprosthesis, insufficient fixation, toxic reactions to the bone cement and implantation of wrong sized endoprosthesis. Some of the early post-operative complications that can occur are venous thromboembolism, joint-stiffness, hematoma or bedsores.

1.2.2.1 Aseptic loosening

Today the most common reason for failure of TJA is aseptic loosening (Sharkey et al. 2014) (Ulrich et al. 2008). In contrary to septic loosening, aseptic loosening occurs when there is no clinical or laboratory proof of

infection. Several theories concerning the causes of aseptic loosening have been developed over the past years, with the conclusion that aseptic loosening has a multifactorial aetiology, including micro-motion, wear mechanisms, high fluid pressure and patient related risk factors (Sundfeldt et al. 2006). Particularly, nanoparticles, generated by wear mechanisms, cause an immune response that leads to bone remodelling processes and eventually wear-induced osteolysis and loosening of the endoprosthesis (Jiang et al. 2013). Phagocytosis of the wear particles by macrophages is considered the beginning of these processes. Secretion of osteomodulating mediators, proinflammatory cytokines and reactive nitrogen and oxygen species maintains the inflammatory process around the implant (Bitar, Parvizi 2015). The inflammatory process is further promoted then by the production of monocyte chemotactic protein 1 (MCP-1), which triggers the acquisition of more and more monocytes (Hallab, Jacobs 2017). The release of cell differentiation factors like receptor activator of NF-κB ligand (RANKL) and monocyte colony-stimulating factor (M-CSF) after ingestion of prosthetic wear particles also lead to a differentiation of local macrophages and monocytes into osteoclasts (Sundfeldt et al. 2006). Furthermore, the phagocytosis of wear particles like cobalt or nickel ions results in an overshooting production of reactive oxygen species, that can interfere with DNA replication and repair mechanisms, leading to a decreased cell activity or even destruction. These actions lead to a continuous osteolysis of the bone, that is surrounding the implant surface (Sansone et al. 2013) (Loeffler et al. 2020).

Patient-related risk factors for the development of aseptic loosening are the male sex, young age, higher activity levels and tobacco use (Bordini et al. 2007) (Inacio et al. 2013) (Kapadia et al. 2014). Interestingly the risk for revision surgery is increased in younger patients. This phenomenon can be explained by higher activity levels in younger generations that result in higher wear rates (Prokopetz et al. 2012). A non-patient related risk factor that is associated with higher rates of aseptic loosening is the mispositioning of the acetabular cup, that leads to undistributed weight bearing and loosening of the endoprosthesis (Traina et al. 2009). Aseptic loosening is considered as a complication, that leads to clinical symptoms of pain, instability or loss of function and eventually revision surgery. The diagnosis of aseptic loosening can be based on clinical symptoms and on radiological signs like progressive

osteolysis at the bone-implant interface or visible migration of the prosthesis. If radiographs do not show clear results, additional bone scintigraphy can detect higher bone metabolism rates as an indicator for aseptic loosening.

1.2.2.2 Septic loosening

When there is a clinical or laboratory proof for infection in a loosened prosthesis, the diagnosis of a periprosthetic joint infection (PJI) or septic loosening, one of the most common reasons for revision in TJA, can be stated (Ulrich et al. 2008) (Sharkey et al. 2014). The pathogenesis of PJI is not entirely known, but it is generally recognized, that the formation of bacterial biofilms is the cause for PJI (Costerton et al. 1999). Bacterial colonization of implants is facilitated by proteins like e.g. fibrinogen, that cover the implant surface after contact with bodily tissues and blood. These proteins function as a conditioning film, that allows the bacteria to adhere to the surface (Schierholz et al. 2004). The bacteria then begin to replicate and when a specific amount, a quorum, is reached, communication between bacteria via quorum sensing molecules is conducted and an extracellular polymer matrix, a living space, where communication and horizontal gene transfer takes place, is formed (Williams et al. 2007) (Flemming, Wingender 2010). The formation of the biofilm induces a local immune response reaction with the activation and migration of phagocytes. The phagocytes secrete chemokines, proteolytic enzymes as well as bactericidal substances. These substances lead to a higher permeability of blood vessels and the promotion of a local inflammatory reaction, that leads to the typical symptoms like calor, rubor, dolor and tumor. The secretion of chemokines also induces the differentiation of human monocytes to osteoclasts, thus leading to local pathological bone resorption (Mörmann et al. 2008).

Periprosthetic joint infection can be divided into late-onset and early-onset PJI according to time of outbreak of the infection after primary implantation or regarding state of the infection into high-grade and low-grade infections. Especially low-grade infections are difficult to diagnose, and the consequences of unnoticed PJI are severe. The main causes for the infection of an artificial joint are haematogenous bacterial colonisation or surgical site infection. Risk factors associated with PJI are the male sex, obesity or coronary artery disease as well as prolonged operation time, urinary tract

infection or former revision surgeries (Triantafyllopoulos et al. 2018) (Pulido et al. 2008a) (Maoz et al. 2015). PJI puts a huge burden on the health care system and reduces the patient's quality of life significantly. Therefore, thorough diagnostics are necessary to prove bacterial contamination in loosened prosthesis. Possible symptoms of an infected joint are fever, local swelling, flush and pain as well as loss of function. In chronically infected joints the development of a syrinx, that connects the infected joint with the skin surface, can occur. If the patient shows signs of an infected joint, further diagnostics should be initiated. Laboratory diagnostics can reveal elevated blood sedimentation rates, CRP-, procalcitonin and white blood cell levels. If possible synovial fluid or tissue samples gathered during sterile puncture or open lavage of the joint should be cultured and analysed to prove bacterial contamination and to identify bacterial flora (Ting, Della Valle 2017). According to a study by Siu et al., the most common causative organisms in PJI were Staphylococcus spp., Streptococcus spp. and Escherichia coli (Siu et al. 2018). Currently, tissue cultures are the gold standard for the diagnosis of PJI, but recent methods such as swab polymerase chain reaction, that shows a higher sensitivity compared with tissue cultures, may supersede them (Omar et al. 2018). Different approaches, that are still under development are detecting PJI via the use of synovial fluid biomarkers or identifying causative organisms via microarrays. According to a study by Deirmengian et al., biomarkers like alpha-defensin or lactoferrin e.g. showed promising results in detecting PJI and they might become an important tool for the diagnostical process of PJI (Deirmengian et al. 2014). In addition to laboratory and microbiological diagnostics, radiographs can reveal signs of prosthetic loosening in PJI. Further imaging diagnostics like a scintigraphy can show higher bone metabolism rates around an infected endoprosthesis. The treatment of PJI can be very challenging. Antibiotic treatment in combination with arthroscopic debridement or lavage can be necessary. But often these techniques do not prevent the progression of PJI, if not a revision operation is needed. For infected endoprosthesis, there often is a two staged revision, meaning that during the first surgical treatment the infected endoprosthesis is replaced with an antibiotic coated spacer, which is then during the second surgical treatment replaced with a new functional endoprosthesis. This procedure is not only highly cost-intensive, it is also

associated with a higher risk of postoperative mortality and morbidity compared to revision surgeries duo to other reasons (Boddapati et al. 2018).

1.2.2.3 Periprosthetic fracture

According to the Swedish national joint registry, periprosthetic fracture is the third most common reason for revision surgery in THA (Lindahl et al. 2005). It is increasingly common and difficult to treat. The aetiology of periprosthetic fractures is either an intra-operative fracturing of the femoral bone when inserting primary endoprosthesis or, as in most cases, a low-energy fall from sitting or standing heights (Lindahl et al. 2005). Risk factors for the development of periprosthetic fractures are age, female sex and poor bone quality because of osteoporosis or malign osteolysis. These conditions lead to more fragile bones (Lindahl 2007). In combination with the higher risk of fall in elderly people, periprosthetic fracture is a considerable threat to TJA and the patients' QoL (Shields et al. 2014). Symptoms of periprosthetic fracture can include loss of function or pain. Radiographs are used to assure the diagnosis of periprosthetic fractures. Radiolucent lines around the prosthesis or bone cement are an indication for periprosthetic fractures. In some cases, computed tomography scans provide further visualisation of fracture lines and evidence for prosthetic loosening. The Vancouver classification, developed by Duncan and Masri, categorises periprosthetic fractures after THA according to the level of fracture and presence of a fixed or loosened endoprosthesis (Duncan CP 1995). Periprosthetic fractures of the knee joint are less common and a meta-analysis by Rhee et al. shows, that a standardised classification system is missing (Rhee et al. 2018). The therapy of periprosthetic fractures is often surgery and if artificial joint parts are loosened revision surgery is required.

1.2.2.4 Implant breaking or component failure

According to a study by Ulrich et al., component failure was the reason for revision in 2.1% of analysed THA (Ulrich et al. 2008). Component failure is an unusual reason for revision, for metal and ceramic materials should withstand high loads and show good mechanical properties. Nonetheless, over a time period those materials can fail and as mentioned earlier, the breaking of the implant was a problem especially in early generation ceramics. The most vulnerable part for component failure in TKA and THA

still remains the PE bearing, that might become brittle due to aging or eventually breaks after wearing out. The symptoms of component failure can include persistent pain and loss of function. Radiographs and computed tomography scans can help identifying breaking of the implant. Revision surgery is indicated in broken implants.

1.2.2.5 Other reasons

The several other reasons for revision surgery are summarised in this chapter. Those include instability, pain or motor deficit, arthrofibrosis, luxation or adverse reactions to metal debris.

Instability is a common reason for revision in TKA and THA (Ulrich et al. 2008) (Sharkey et al. 2014). An analysis by Wilson et al. revealed, that instability was frequently reported in younger patients and most commonly in female patients (Wilson et al. 2017). It can arise from polyethylene wear, component loosening or breaking, ligamentous instability or surgical error in relation to the implant size. Instability can be treated by correcting the problems of malalignment that results from the causative factors. Constrained implants are a valuable treatment option for TKA patients with instability (Vince et al. 2006).

Arthrofibrosis is a complication of a trauma or manipulation associated with an excessive production of fibrous scar tissue, which can present with a warm or swollen joint, a loss of range of motion and painful stiffness (Manrique et al. 2015). Risk factors for the development of arthrofibrosis include genetics, decreased preoperative range of motion and higher complexity surgery (Gandhi et al. 2006) (Hold et al. 2009). The treatment options for arthrofibrosis include physiotherapy, manipulation under anaesthesia, arthroscopic or open debridement, also known as lysis of adhesions, and, as a final treatment option if previous measures have failed, revision TJA (Cheuy et al. 2017).

Luxation or dislocation is a phenomenon that can occur especially in THA. It often leads to pain, stiffness and loss of function. Reasons for luxation can be the mispositioning of the stem or acetabular part or mobilisation therapy in patients with weak muscle security. Usually a luxation occurs in early postoperative stages, since over time a solid capsule around the artificial joint is regenerated providing stability. PE wear is a risk factor for late dislocations,

since the nanoparticles can cause inflammatory response reactions, leading to a thinning of the pseudo-capsule and a higher risk for dislocation (Knoch et al. 2002) (Parvizi et al. 2006).

Adverse reactions to metal debris (ARMD) describe a local hypersensitivity reaction to metal debris with the formation of pseudo-tumours (Willert et al. 2005). The definition of ARMD includes pseudo-tumours, periprosthetic osteolysis and necrosis (Pandit et al. 2008a) (Pandit et al. 2008b). Its aetiology is not completely discovered, but it is associated with biologically active, nanometre sized particles from the MoM bearing surfaces (Lohmann et al. 2013). According to a study by Doorn et al., MoM articulations generate approximately 6.7 × 1012 to 2.5 × 1014 particles every year, which is 13.500 times the number of PE particles produced from a MoP bearing (Doorn et al. 1998). Risk factors for ARMD include the female gender, design of the components, small femoral component size and acetabular component malposition (Haan et al. 2008) (Glyn-Jones et al. 2009).

In addition to local effects like pseudo-tumour development, elevated blood metal ion levels are frequently attested in patients with MoM bearings. The release of cobalt is due to the mechanical and oxidative stresses placed on the prosthetic joint. Especially in patients with larger femoral head sizes, blood ion levels are significantly increased, allowing the assumption, that the design of the implant affects serum ion levels (Matharu et al. 2015). Although systemic effects of metal toxicity are rare, patient cases with systemic symptoms have been reported. Systemic cobalt intoxication presents with various neurological, cardiovascular and endocrine symptoms (Leyssens et al. 2017). Even in functioning MoM arthroplasties elevated blood ion levels can be detected. The cut-off level for identifying failing MoM bearings was set to >5 µg/l for cobalt and chromium ions in blood serum (Hart et al. 2011). Interestingly the metal ion levels do neither correlate with the presence of pseudo-tumours nor with the severity of local tissue reaction (Williams et al. 2011). If a patient shows elevated metal ion levels, a symptomatic MoM arthroplasty or the development of a pseudotumor, revision surgery is indicated (Kwon et al. 2014).

1.2.3 Problems of revision surgery

The expansion of the indication for primary TJA to younger and more active patients as well as an increasing rate of primary TJA generally, lead to higher rates of revision TJA. Revision surgery is not only a potential threat to the patient`s health but also puts a huge burden on the healthcare system. This chapter aims at portraying the problems of revision TJA. A study by Bozic et al. analysing revision TJA between 2005 and 2010 showed, that revision surgery in TKA has increased more than revision in THA. But revision THA has a greater effect health-related and economically with higher costs and longer in-hospital stays. Revision surgery due to PJI is associated with the highest costs (Bozic et al. 2015). In a former analysis, Bozic et al. compared primary to revision THA at a single institution. They were able to show that revision surgery was associated with higher costs, higher risk for complications, longer mean operative time and a longer mean length of hospital stay when compared to primary THA, concluding that the hospital resource utilization for revision THA was significantly higher than for primary THA (Bozic et al. 2005). Several other studies specified the patient related complications, indicating that there is a higher risk for dislocations, venous thromboembolism and infections in revision TJA, when compared to primary TJA, resulting in a higher mortality rate in revision TJA (Pulido et al. 2008b) (Khatod. M. et al. 2006) (Mahomed et al. 2003). Furthermore, the risk of subsequent revision surgery is higher in patients who underwent their first revision surgery when compared to patients who underwent primary TJA, thus there is an even higher threat and higher risk of complications in patients who undergo revision surgery (Ong et al. 2010). Studies by Patil et al and Lübbeke et al. investigated the QoL and satisfaction levels in patients who underwent primary and revision THA. They discovered that the postoperative functional outcome, improvement in QoL and satisfaction is greater for patients with primary THA than for patients with revision THA. A possible explanation for this is the higher complication and morbidity rate in patients undergoing revision surgery (Patil et al. 2008) (Lübbeke et al. 2007).

In conclusion, there are various reasons for revision surgery that can affect the patients QoL. First of all periprosthetic joint infections that increase the mortality rate in affected patients significantly. For the prevention of

postoperative complications after primary TJA the assessment of certain risk factors that lead to revision surgery is important. It is clearly visible, that compared to primary TJA, revision TJA carries a huge burden not only for patients but also for the health care system with immense costs. A study by Sharkey et al. reports, that the reasons for revision surgery have changed over the last decades (Sharkey et al. 2014). To contribute to modern day research in the field of revision surgery, the underlying statistical analysis of this thesis aims at identifying risk factors and preoperative conditions, that lead to a higher risk of revision TJA. A statistical analysis of 335 revision TJA cases, that were performed during the years 2011 and 2016 at the department of orthopaedic surgery at the university hospital of Magdeburg, was carried out. The aim of the study was to investigate possible changes in the reasons for revision of hip and knee TJA and to identify certain risk factors, that lead to the failure of TJA. The methods and results of that study will be portrayed throughout the following chapters.

2. Material and Methods

2.1 Patients and implants

A systematic retrospective study of 335 revision TJA (177 total hip arthroplasties and 158 total knee arthroplasties) that were performed at the department for orthopaedic surgery of the University of Magdeburg, in the years 2011 (169 revision TJA) compared to 2016 (166 revision TJA) was performed. The study was approved by the institutional Review Board of the Faculty of Medicine of the Otto-von-Guericke University (IRB No 106/17). The exclusion criteria included patients with revision operations of antibiotic coated spacers.

The department for orthopaedic surgery of the University of Magdeburg manages an implant storage, where explanted implants are preserved and sorted by the year and months of explantation. Available implants, extracted in the years 2011 and 2016, were decontaminated and cleaned immediately after revision surgery by the central sterilisation department of the clinic. Therefore, a washer-disinfector (Miele Professional, Gütersloh, Germany) performed an automated disinfection program at 99°C for 10 minutes followed by a rinsing process with demineralised water at 93°C and a 20-minute drying process. In certain cases, further cleaning was needed to withdraw adhering organic material using warm water and the cleaning detergent 10ml/l Neodisher Medicalen forte (Dr. Weigert, Hamburg, Germany). An X-ray fluorescence analyser (Bruker, S1 Titan Series, Bruker Corp., Billerica, USA) was applied to determine the used chemical composition of the metallic implant components. The compiled materials were cobalt-chromium-alloy, titanium and iron-based alloys. The fastening method was either cemented or cementless.

In addition to that, patient cases were examined. Access to the patient files was granted via the local network of the department for orthopaedic surgery of the University of Magdeburg. The programs, that were used for gathering the relevant data, were medico and HypOrth. Through these software case histories, general letters, microbiological reports, histological findings, specific blood parameters, surgery reports, radiographs and reports, as well as anaesthetic protocols were accessible and considered. Detailed patient characteristics, that were relevant to classify demographics such as sex, age and BMI, was collected as well as general characteristics about former

arthroplasties, former infection, CRP levels, implantation time and use of bone cement during the implantation. Comorbidities including rheumatoid arthritis, Diabetes mellitus type 1 and 2; reduced glomerular filtration; high blood pressure and immunosuppression were recorded. All the above-mentioned characteristics were included in the risk factor analysis.

2.2 Implant failure analyses

Failure mechanisms were determined by review of patient files, surgery reports and radiographs. If there were cases with multiple reasons for failure, the primary reason was selected by decision of the author. Failure due to aseptic loosening was attested in loosened implants with no evidence for bacterial infection in tissue cultures or histological findings. Verification of infection in implants via tissue cultures or pathological findings was necessary to assign the patient cases to the periprosthetic joint infection group. Periprosthetic fracture cases were detected through radiographs and reports that indicated a fracture to the adjacent bone of the prosthesis. When radiographs showed a breaking of the implant or the surgeon reported this phenomenon, cases were classified in the group of breaking of the implant. Other failure mechanisms like arthrofibrosis, instability, pain, mispositioning or motor deficit were determined by reviewing case histories, patient symptoms and operative reports. A luxation was determined by reviewing radiographs and reports (figure 1). Metal intoxications as well as failure due to ARMD were detected by reviewing patient cases and blood cobalt levels. For the statistical analysis, the determined reasons for revision were pooled in five groups. The compiled reasons for revision were aseptic loosening, septic loosening, periprosthetic fracture, breaking of the implant, and others, which included luxation, instability, arthrofibrosis, ARMD or metal intoxication, pain, motor deficit and mispositioning.

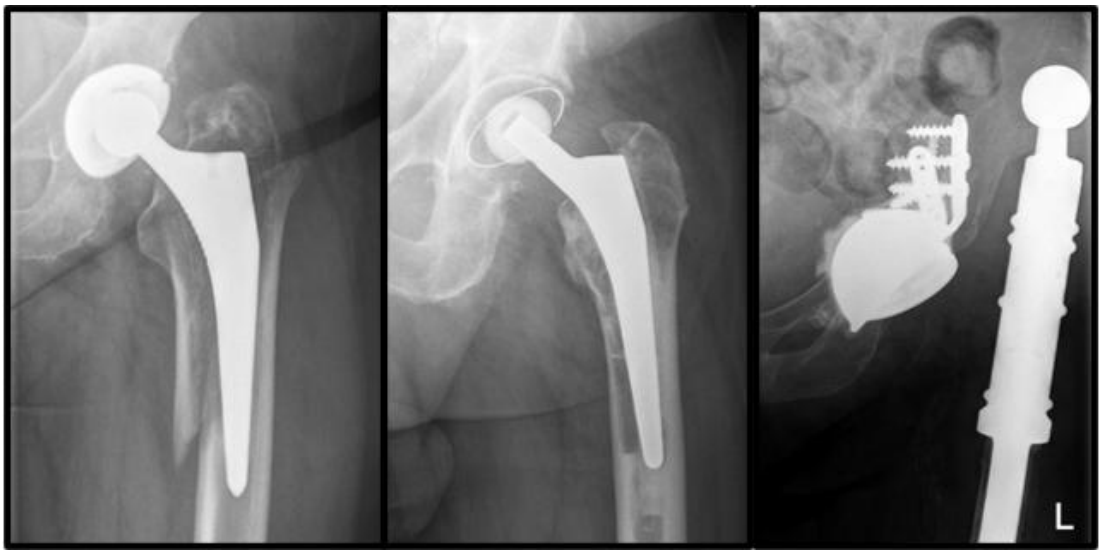

Figure 1: left: radiograph showing a periprosthetic fracture of the femur; middle: radiograph showing osteolytic lesions in a femur; right: radiograph showing luxation of a THA

2.3 Database

All data, and additionally to that, pictures of the analysed implants, were entered into a database (MS Access), allowing comparison between groups and determination of relationships between the different variables. The pictures were taken with a single lens reflex camera, portraying not only the size and type of the endoprosthesis but also the pattern of destruction (figure 2). The database was split into two main sections: a THA and a TKA section. Each of these two sections was then subdivided and data regarding design, size, bearing materials as well as reason for revision and potential risk factors were added (figure 3).

Figure 2: Representative photographs of retrieved TJA, top left: signs of wear in a ball head of a THA; top right: signs of wear and destruction of the inlay in a tibial part of a TKA; bottom left: fracture of the acetabular component of a THA; bottom right: corrosion of the taper of a THA

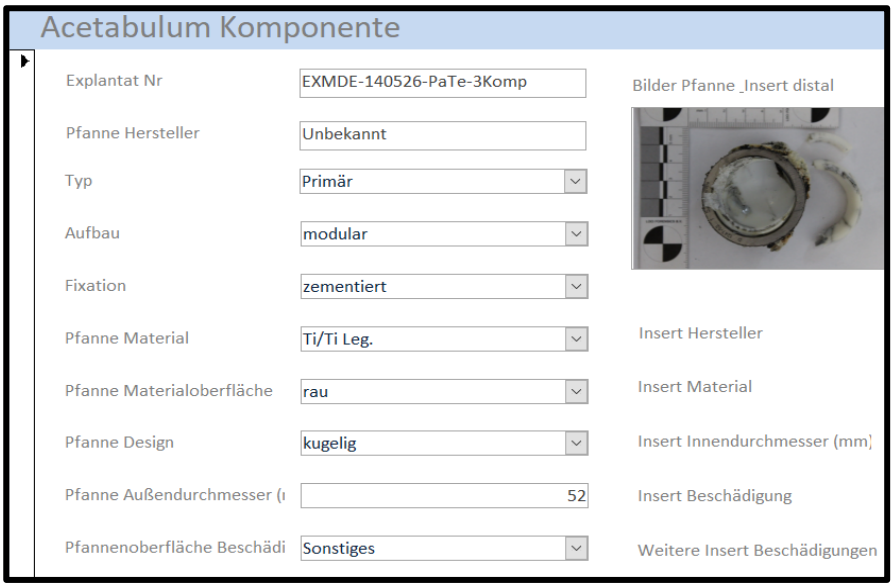

Figure 3: Representative picture of the database

2.4 Statistical analysis

The statistical analysis was performed using SPSS 25. To compare the reasons for revision in the years 2011 and 2016, the chi-square test was applied. To identify possible risk factors for PJI, a univariate analysis was performed. Factors that showed significant results underwent a logistic regression analysis to rule out interaction effects. Variables with a $p \leq 0.05$ were deemed significant risk factors for the development of PJI.

3. Results

3.1 Description of the cohort

335 revision TJA were included in this study. Out of these patients 135 were male, and 200 were female. The average age of male patients was 68,9 years (range 22-87 years) and the average age of female patients was 69,1 years (range 39-88 years) at the time of revision TJA. The average body mass index was 30.24 (kg/m²) in female patients and 29.73 (kg/m²) in male patients. Revision surgery was conducted for 177 THA (88 in 2011 and 89 in 2016) and for 158 TKA (81 in 2011 and 77 in 2016). The mean year of implantation in the group of 2011 was 2005 (range 1980-2011). In the group of 2016, it was 2010 (range 1984-2016). The average time of implantation in female patients was 78.63 months and in male patients 54.61 months (table 1).

	male	female	total
revision TJA	135	200	335
revision TKA	61	97	158
revision THA	74	103	177
average age (years)	68.9	69.1	69
average time of implantation (months)	54.61	78.63	68.91
average BMI (kg/m²)	29.73	30.24	30.04

Table 1: demographic data of the whole cohort

3.2 Changes in the reasons for revision

In a first analysis the reasons for revision of the year 2011 were compared to those of the year 2016. In the year 2011, out of 169 revision operations, 58 (34.3%) were due to aseptic loosening, whereas 47 (27.8%) were due to septic loosening, 46 (27.2%) due to other reasons, 12 (7.1%) due to periprosthetic fracture and only 6 (3.6%) were due to breaking of the implant. The percentage which were due to other reasons was made up of 17 (10.1%) revisions due to arthrofibrosis, 12 (7.1%) due to luxation, 10 (5.9%) due to instability, 6 (3.5%) due to a motor deficit and just 1 (0.6%) due to pain.

In the year 2016, out of 166 revision operations, 55 (33.1%) were due to septic loosening, 46 (27.7%) due to aseptic loosening, 40 (24.1%) due to other reasons, 21 (12.7%) due to periprosthetic fracture and 4 (2.4%) were

due to breaking of the implant. Again, the percentage which was due to other reasons was made up of 16 (9.6%) revision operations due to luxation, 9 (5.4%) due to instability, 6 (3.6%) due to metal intoxication, 4 (2.4%) due to arthrofibrosis, 3 (1.8%) due to a motor deficit, as well as 1 (0.6%) due to pain and 1 (0.6%) due to mispositioning (figure 4).

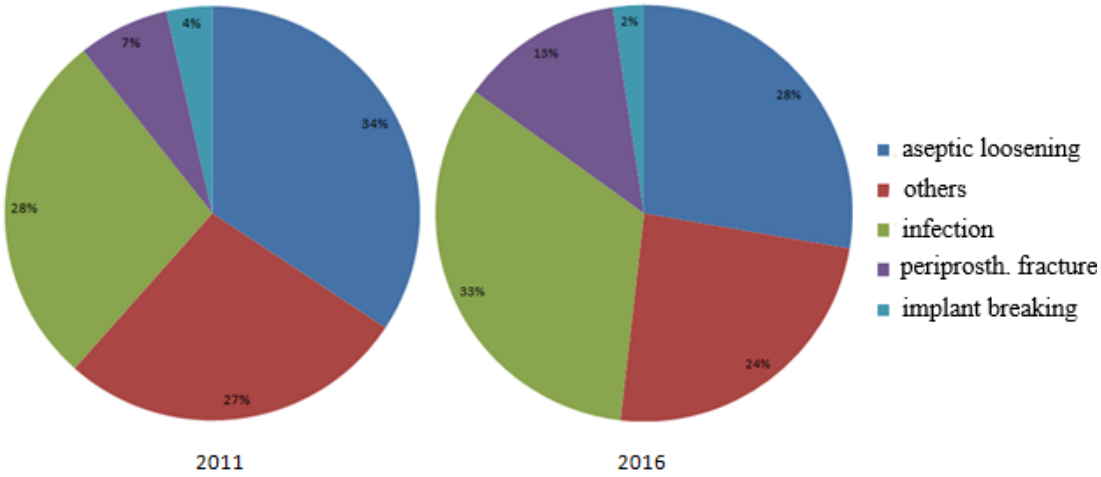

Figure 4: Percentage of patients for each failure mechanism for the years 2011 (4a) and 2016 (4b)

Even though the absolute numbers for each revision cause varied, the reasons for revision in the year 2011 compared to the year 2016 showed no significant difference (p=0.262) using the chi-square test. There were minor differences in the group of “other reasons”, which were not included in the statistical analyses due to very low case numbers. For example, the failure mechanism of metal intoxication was found in 6 cases in 2016 but did not show up in the year 2011. There was also a difference in cases of arthrofibrosis, with 4 patients in 2016 and 17 patients in 2011. A specific analysis of 54 THA cases of revision due to aseptic loosening of the whole cohort revealed that the acetabular component was loosened in 31 (57,4%) patients and only the femoral stem was loosened in 16 (29,6%) cases. Both, acetabular and femoral stem component, were loosened in 7 (13%) cases.

Further analysis to investigate the influence of bearing materials as well as femoral head sizes on the reasons for revision were conducted. The analysis regarding the articulating materials of the examined implants revealed, that out of 86 THA pairings of 2011 and 2016, 62 (72,1%) were ceramic-on-polyethylene, 22 (25,6%) metal-on-polyethylene, as well as 1 (1,15%) ceramic-on-ceramic and 1 (1,15%) metal-on-metal pairings (figure 5). The implemented statistical analysis showed no significant correlation between any articulating material and the actual reason for revision. A more specific inspection of the influence of articulating material and the incidence of aseptic loosening (p=0,384) or septic loosening (p=0,565) also showed no significant results.

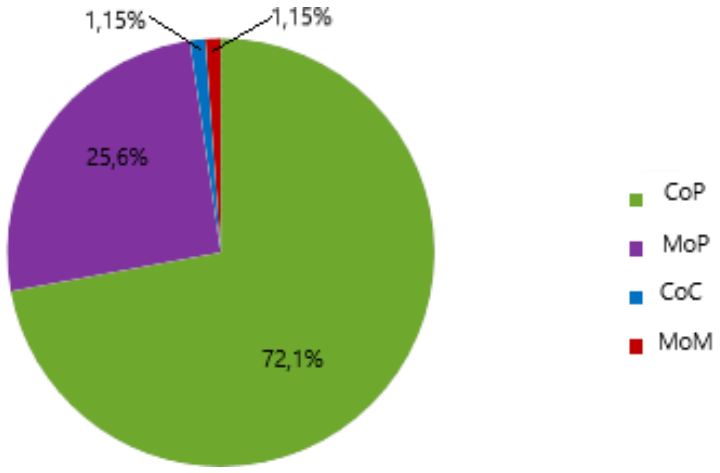

Figure 5: Percentage of articulating surfaces in a cohort of 86 cases

The correlation between the femoral head size and the reason for revision was investigated as well. Out of 162 included THAs of 2011 and 2016, the femoral head size was 32 mm in 107 (66,05%) cases, bigger than 32 mm in 24 (14,8%) cases and smaller than 32 mm in 31 (19,15%) cases (figure 6). The statistical analysis using the chi-square test again revealed no significant correlation between size of the femoral head and reason for revision (p=0,394). A specific inspection of the influence of larger femoral head size on the incidence of aseptic loosening (p=0,226) and the effect of smaller femoral head size on the incidence of luxation (p=0,43) revealed no significant results either. However, there is a significant effect of the smaller femoral head size (<32 mm) on the occurrence of aseptic loosening (p=0,024).

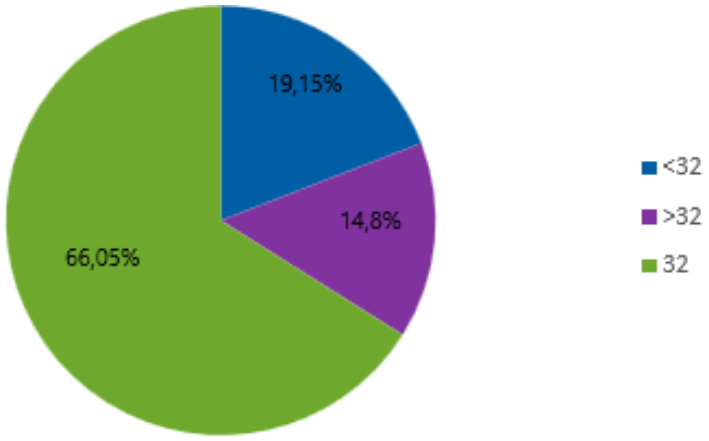

Figure 6: Percentage of femoral head sizes (mm) in a cohort of 162 cases

3.3 Risk factor analysis

No significant difference regarding the reasons for revision in the years 2011 and 2016 was detected, however the infection rate clearly succeeded the rate for aseptic loosening in the year 2016. Because of the present concern about PJI and to further investigate why the infection rate has increased in the year 2016, the decision was made to conduct a multivariate risk factor analysis for the development of PJI with a combined cohort of both years. A survey of the demographic data revealed that out of the 335 revision cases, 102 were due to septic loosening. All together the infection cases consisted of 41 female patients and 61 male patients, whereas the remaining 233 cases without an infection consisted of 159 female patients and 74 male patients (table 2).

	infection	no infection	total
2011	47	122	169
2016	55	111	166
male	61	74	135
female	41	159	200

Table 2: Demographic aspects of the cases with PJI

In a next step a univariate analysis to analyse the effect size of each of the above-mentioned parameters on the occurrence of infection was performed. Table 3 shows the univariate analysis for proposed infection risk factors. The material of the endoprostheses showed no significant correlation with the

infection risk. Possible risk factors for the development of PJI in the univariate analysis were sex ($p<0.001$), former PJI ($p<0.001$), reduced glomerular filtration ($p=0.003$), Diabetes mellitus ($p=0.013$) and high blood pressure ($p=0.031$) (table 3). To confirm these results, a multivariate logistic regression analysis was performed for all comorbidities and characteristics that achieved a significant p-value ≤ 0.05 in the univariate analysis (table 3). The following multivariate analysis not only revealed that patients, who already suffered from a former PJI, have a significantly higher risk of developing a PJI ($p<0.001$). Notably, it also reveals a striking correlation between the male sex and the development of PJI ($p<0.001$) (table 3). In addition to that, a risk analysis revealed, that a male person has a 3.197 times higher risk for the development of PJI than a female patient (OR=3.197) and a patient who already suffered from a PJI has a 6.133 times higher risk for the development of a PJI than a patient who never had a PJI (OR=6.133).

comorbidities or characteristic	univariate analysis, p-value	multivariate analysis, p-value	odds ratio
male gender	**<0.001**	**<0.001**	**3.197**
former infection	**<0.001**	**<0.001**	**6.133**
BMI <18/>40 (kg/m²)	0.822		
coronary artery disease	0.118		
reduced glomerular filtration	**0.003**	0.07	
Diabetes mellitus (Type 1 or 2)	**0.013**	0.173	
high blood pressure	**0.031**	0.221	
osteoporosis	0.415		
intake of immuno-active substances	0.640		
use of PMMA	0.118		
use of iron	0.104		
use of titanium	0.674		
use of cobalt-chromium	0.096		

Table 3: Univariate and multivariate risk factor analysis for the development of a PJI

To support the findings of a higher rate for infection in male patients, a further analysis regarding the mean C-reactive protein (CRP) levels in the male cohort compared to the female cohort was conducted. Using a t-test the analysis showed a significant increase in CRP levels of male patients compared to female patients (p=0.031). A mean CRP level of 41.27 (mg/l) in the male group and 26.52 (mg/l) in the female group was detected (figure 7). These results are in line with the formerly detected shorter time of implantation in the male sex.

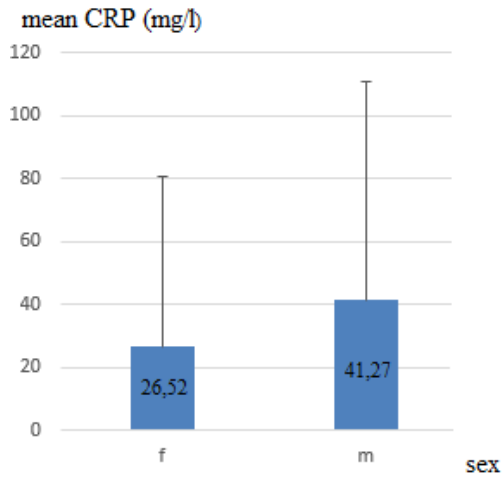

Figure 7: mean CrP-level (mg/l) in male and female patients

Because of the correlation between male sex and infection and to further illustrate those findings, the entire cohort was then divided into male and

female patients and the reasons for revision were analysed again. Figure 8 depicts the most common failure mechanisms for male patients compared to female patients. By using the chi-square test a highly significant difference between the reasons for revision in male and female patients ($p<0.001$) was identified. The most common aetiology of failure in the male sex is, by far, septic loosening. Out of 135 revision TJA in male patients, 61 (45.2%) were due to infection, 38 (28.1%) due to aseptic loosening, 27 (20%) due to other reasons, 7 (5.2%) due to periprosthetic fracture and 2 (1.5%) revision operations were due to breaking of the implant.

Compared to the male patients, the infection rate in the female sex is relatively low. Aseptic loosening is in this group the most common aetiology of failure. Also, the rate for periprosthetic fracture is considerably higher in female patients. Out of 200 revision TJA in female patients, 66 (33%) were due to aseptic loosening, 59 (29.5%) due to other reasons, 41 (20.5%) due to infection, 26 (13%) due to periprosthetic fracture and 8 (4%) revision operations were due to breaking of the implant (figure 8).

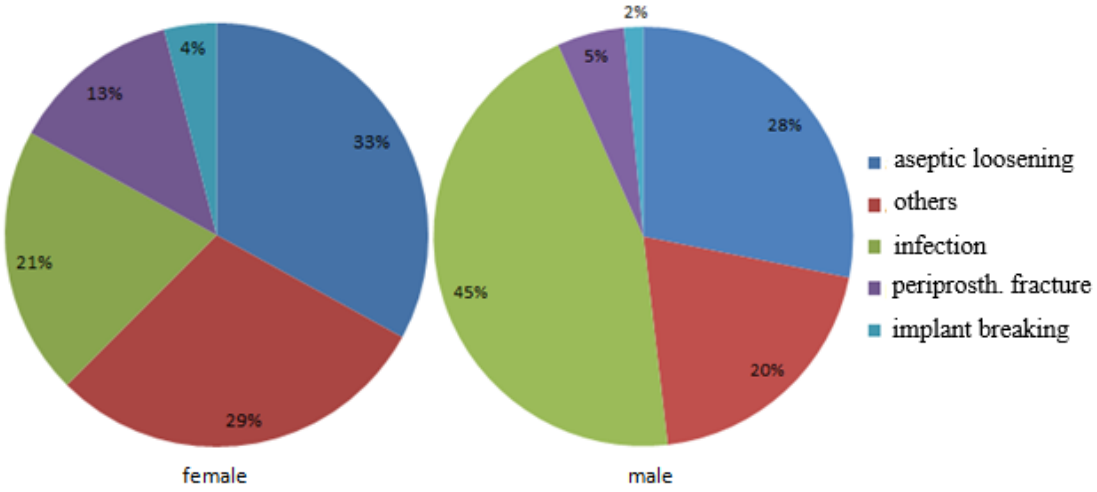

Figure 8: Most common reasons for revision in female and male patients of the cohort

4. Discussion

The study revealed that there is no significant difference in the reasons for revision of TJA in the year 2011 compared to the year 2016. However, there is a highly significant difference between male and female patients. Male patients have a significantly increased risk for the development of a PJI. Compared to the numbers of primary TJA, the incidence of revision surgeries is relatively low. Nonetheless the potential threat of revision TJA to the patients' health and the health-care system is immense (Kurtz et al. 2012). According to the results, the reasons for revision have not changed over a five-year period spanning from 2011 to 2016. Aseptic loosening, septic loosening and periprosthetic fracture were the most common reasons for revision in general. This is in line with studies by Reina et al. showing similar results in primary total hip arthroplasty revision cases (Reina et al. 2013). Notably, the study also shows that the biggest risk factor of loosening was dependent on the patient`s sex. While in female patients aseptic loosening was the most common reason for failure, it was septic loosening in male patients. A correlation between the sex of the patient and the infection rate was also identified by Reina et al. (Reina et al. 2013) or Bozic et al. (Bozic et al. 2012). Furthermore, the study revealed that the rate for periprosthetic fracture was more than two times higher in female patients when compared to male patients. That revision cases due to periprosthetic fracture were more often found in female patients, was also described by Toogood and Vail (Toogood, Vail 2015). The reason for these findings can be traced back to a higher incidence of osteoporosis in female patients.

The overall incidence of infection in the study was 30.4%. Similar results have also been reported by others. Sharkey et al (Sharkey et al. 2002) identified an infection rate of 27.4% in their studies about revision TKA and pointed out, that infection was the most common mode of failure in the early revision group (<2 years of implantation time). Similar results with infection rates in revision TKA of 30% were provided by Hossain et al (Hossain et al. 2010). The investigation shows an increased percentage of revision cases due to PJI in 2016 compared to 2011. Comparable results were produced by Lenguerrand et al., showing that infection rates are increasing in revision THA (Lenguerrand et al. 2017). Other studies meanwhile report aseptic loosening and polyethylene wear accounting for 38% of all revisions as the

most common reasons for revision knee endoprosthesis (Sheng et al. 2004) (Sharkey et al. 2002). Furthermore, in a recent study Sharkey et al. investigated the changes in the reasons for revision surgery in TKA and discovered, that polyethylene wear was no longer the major cause of failure (Sharkey et al. 2014). Their study highlights, that there is a shift in the percentage of revision reasons, presumably due to the improvements in the quality of materials, that are used for TJA.

The study included common risk factors in the analysis and thus was able to validate existing results for the factors sex and prior PJI (Bozic et al. 2014) (Poultsides et al. 2018). The study showed that male patients have a 3.197 times higher risk for the development of PJI in TJA when compared with female patients. The male sex as a potential risk factor for the development of PJI in THA was also detected by Bozic et al. and described by Cochran et al. for revision TKA (Bozic et al. 2014) (Cochran et al. 2016). Studies about sex differences in the immune system might present an answer to this occurrence. Sex hormones have a specific influence on the regulation of the immune system, affecting the outcome of inflammatory or autoimmune diseases (Oertelt-Prigione 2012). Bouman et al. stated that female patients are more resistant to infections and have a higher incidence of autoimmune diseases (Bouman et al. 2005). This thesis delivers a possible explanation for the higher infection rate in male patients.

The study also showed that patients who already suffered from a PJI have a 6.133 times higher risk for the development of a PJI than patients that never underwent a PJI. Similar results were detected by Bedair et al. (Bedair et al. 2015). There are several studies that describe an elevated BMI and its consequential comorbidities as a risk factor for the development of a PJI. Maoz et al. for example identified an BMI > 40 kg/m^2 as a significant factor (Maoz et al. 2015). In the underlying study the BMI could not be confirmed as a risk factor for PJI, it is to be noted however, that the mean BMI of male and female patients of the cohort was in the range of overweight.

The performed study revealed that there was no significant connection between the articulating surfaces and the reason for revision. Results found by Wang et al., who were able to show, that ceramic-on-polyethylene bearing surfaces had a lower wear rate than metal-on-polyethylene surfaces, indicate however a higher rate for aseptic loosening in MoP bearing surfaces (Wang

et al. 2013b). A study by Byström et al. with data from the Norwegian Arthroplasty Register showed, that with smaller femoral head sizes the risk for luxation is increased, compared to larger femoral head sizes (Byström et al. 2003). These findings add to results by Amstutz et al., who were able to show, that with larger femoral head sizes a greater range of motion can be achieved while lower risk of luxation (Amstutz et al. 1975). In the underlying study, no correlation between femoral head size and risk for luxation was found, which can be due to a very low number of revision cases due to luxation.

It is recognized that there are limitations to this study. The university hospital of Magdeburg is a tertiary referral centre, receiving large numbers of patients with complicated revision cases. Since revision cases due to PJI are usually more complicated, the proportion of infection cases might be higher than expected in general practice. Furthermore, the implants were randomly chosen from the implant storage of the institution. Due to the fact, that patients can demand their extracted implants, this circumstance could lead to the missing of some implants. However, these potentially limiting factors do not influence the risk factor analysis.

In conclusion the study revealed that the reasons for revision did not change over the period from 2011 to 2016. Aseptic and septic loosening were the most common reasons for revision surgery in general. A substantial difference in the reasons for revision when male and female patients were compared, with a significantly higher infection rate in male patients, was discovered. Other studies concerning failing TJA generated similar results. The findings hint at specific sex differences in failing TJA, a possible explanation might be the difference in the immune system with female patients being more resistant to infections. Also, the analysis showed a highly increased risk for septic loosening in patients, who already underwent a revision surgery due to septic loosening. A possible reason for that might be the persistence of bacteria.

Specific antibiotic treatment and careful management of periprosthetic joint infection, especially in male patients and patients who underwent a prior revision surgery is indicated. The findings of the implemented study should be subject to further analysis.

5. Summary

Total joint arthroplasty (TJA) is a very successful surgery and therefore has been labelled as “the operation of the century” (Learmonth et al. 2007). TJA has become a fundamental part of modern orthopaedic surgery, improving the quality of life of patients who suffer from chronic degenerative joint diseases immensely. (Liebs et al. 2016). Due to the demographic changes in society, TJA rates are expected to increase drastically within the next years, pushing the ongoing research to optimize implant materials, surgical techniques and perioperative care to perfection (Kurtz et al. 2007). However, an increased implantation rate is also accompanied by an increase in revision cases. Revision surgeries are a greater burden for the patient as well as the health-care system, compared to primary implantations (Kurtz et al. 2012). There are different reasons for revision surgery, including prosthesis loosening, breaking of the prosthesis or fracture of the adjacent bone, infection or complaints of the patient due to reduced joint mobility or pain. Several studies investigated the reasons for revision for TJA describing either septic or aseptic loosening as the main factor for revision surgery (Ulrich et al. 2008) (Sharkey et al. 2014). Even though the failure mechanisms in TJA have varied and changed over the last decades, they consistently included septic loosening (Sharkey et al. 2014). Revision cases due to septic loosening of endoprostheses are associated with higher rates of mortality and morbidity (Boddapati et al. 2018). Some of the most important risk factors for TJA complications are the age of the patient at implantation time, physical activity and an increased BMI (Ward et al. 2015) (D'Apuzzo et al. 2014). Especially, the risk for infection is associated with the number of prior revision surgeries, as well as comorbidities of the patient (Bozic et al. 2012). The analysis of 335 revision TJA cases, performed during the years 2011 and 2016 at the University hospital of Magdeburg, confirmed some of the most fundamental findings in research on revision surgery. The main reasons for revision surgery in the cohort were septic and aseptic loosening. There is a difference in the reasons for revision between male and female patients, a further analysis of the revision cases due to septic loosening revealed an increased risk for PJI in male patients as well as in patients, that already underwent a revision surgery due to PJI.

Zusammenfassung

Die Versorgung eines Gelenkes durch eine Endoprothese ist ein erfolgreiches Operationsverfahren, welches sogar als Operation des Jahrhunderts bezeichnet wurde (Learmonth et al. 2007). In der modernen Orthopädie nimmt die Gelenkendoprothetik aufgrund der erheblichen Verbesserung der Lebensqualität von Menschen, die an chronisch-degenerativen Gelenkerkrankungen leiden, eine wichtige Rolle ein (Liebs et al. 2016). Bedingt durch den demografischen Wandel ist mit einer Zunahme der Anzahl der durchgeführten Endoprothesenimplantationen zu rechnen. Damit verbunden ist die intensive Suche und das Streben nach den besten Materialien, Operationstechniken oder dem besten perioperativem Management (Kurtz et al. 2007). Eine erhöhte Rate an Endoprothesenimplantationen geht jedoch auch mit einer erhöhten Rate an Revisionsfällen einher. Im Vergleich mit Primärimplantationen stellen Revisionseingriffe von Endoprothesen eine größere Belastung nicht nur für betroffene Patienten aber auch für das Gesundheitssystem dar (Kurtz et al. 2012). Es gibt verschiedene Ursachen für die Notwendigkeit einer Revisionsoperation bei Endoprothesen. Dazu zählen unter anderem die septische und aseptische Lockerung, Materialversagen und -bruch, periprothetische Frakturen, Luxationen oder Beschwerden des Patienten aufgrund persistierender Schmerzen und eingeschränkter Beweglichkeit des betroffenen Gelenkes. Mehrere Studien, welche sich mit Revisionsgründen befasst haben, zeigen, dass septische und aseptische Lockerung die beiden Hauptgründe für das Versagen einer Endoprothese sind (Ulrich et al. 2008) (Sharkey et al. 2014). Sie zeigen außerdem, dass, obwohl sich die Häufigkeiten der einzelnen Revisionsgründe in den letzten Jahrzehnten verändert haben, die septische Lockerung immer einen bedeutenden Anteil hatte (Sharkey et al. 2014). Revisionsoperationen aufgrund von septischer Lockerung sind mit einer höheren Mortalität und Morbidität assoziiert. Einige der häufigsten Risikofaktoren für das Versagen einer Endoprothese sind das Patientenalter, das Level an Aktivität und der BMI (Ward et al. 2015) (D`Apuzzo et al. 2014). Ein erhöhtes Risiko für periprothetische Infektionen ist mit der Anzahl an vorhergehenden Revisionseingriffen sowie den Begleiterkrankungen assoziiert (Bozic et al. 2012). Eine Analyse von 335 Revisionseingriffen, welche in den Jahren 2011 und 2016 an der

orthopädischen Universitätsklinik Magdeburg durchgeführt wurden, konnte einige der oben genannten Erkenntnisse der Revisionsendoprothetik bestätigen. Die Hauptgründe für das Versagen von Endoprothesen in der untersuchten Kohorte waren aseptische und septische Lockerung, es konnte ein Zusammenhang zwischen dem biologischen Geschlecht sowie der prozentualen Verteilung der Revisionsgründe dargestellt werden. Eine genauere Analyse der Fälle von septischer Lockerung zeigte ein höheres Risiko in männlichen Patienten sowie in Patienten/Patientinnen, welche sich bereits einem oder mehreren Revisionseingriffen unterziehen mussten.

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Credits

Die Danksagung ist in der Version aus Datenschutzgründen nicht enthalten.

Declaration of academic integrity

Ich erkläre, dass ich die der Medizinischen Fakultät der Otto-von-Guericke Universität zur Promotion eingereichte Dissertation mit dem Titel

Increased risk for periprosthetic joint infection in male patients – an analysis of 335 revision total joint arthroplasty cases

in der orthopädischen Universitätsklinik der Otto-von-Guericke-Universität Magdeburg

mit Unterstützung durch Herrn Prof. Dr. med. C.H. Lohmann, Frau Prof. Dr. rer. nat. J. Bertrand, Frau M. Herbster sowie das Team der experimentellen Orthopädie der orthopädischen Universitätsklinik Magdeburg

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Curriculum vitae

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