JB&JS OPEN ACCESS

High Rates of Aseptic Loosening After Revision Total Knee Arthroplasty for Periprosthetic Joint Infection

Arne Kienzle, MD, Sandy Walter, Philipp von Roth, MD, Michael Fuchs, MD, Tobias Winkler, MD, and Michael Müller, MD

Investigation performed at Charité University Hospital Berlin, Berlin, Germany

Background: With increasing life expectancy, the demand for knee replacement is continuously rising. Despite the use of antibiotic prophylaxis and improved aseptic surgical techniques, periprosthetic joint infection (PJI) still occurs in 1% to 5% of patients after primary arthroplasty. An open question is the influence of PJI and resulting surgical procedures on the occurrence of long-term complications such as aseptic loosening. Patients needing multiple revision surgeries are especially at risk for decreases in bone mass and damage to the medullary cavity. Thus, we theorized that prior surgeries on the affected knee increase the risk of aseptic loosening in patients with PJI.

Methods: We retrospectively analyzed the cases of 100 patients who underwent total knee replacement exchange surgery as a result of PJI. In addition to clinical, paraclinical, and radiographic examination, we assessed comorbidities and the number of prior surgeries.

Results: Prosthetic survival was drastically decreased after PJI-related revision arthroplasty: during the first 7.3 years after reimplantation, 22% and 16% of all patients had aseptic loosening and recurrent PJI, respectively. The prevalence of aseptic loosening was 27.8% for female and 15.2% for male patients. A significant association between increasing patients' American Society of Anesthesiologists (ASA) classification and prosthetic failure rates was found, as was a strong correlation between number of prior surgeries and aseptic loosening

Conclusions: In this study, we found notable rates of aseptic loosening and recurrent PJI following PJI-related revision arthroplasty. The difference in the rate of aseptic loosening among male and female patients supports theories of the role of bone metabolism in the development of aseptic loosening. The economic and clinical burdens of prosthetic failure make it paramount to gain a better understanding of bone metabolism in PJI. Additional research should address the need to optimize treatment strategies to increase prosthetic survival.

Level of Evidence: Therapeutic Level IV. See Instructions for Authors for a complete description of levels of evidence.

With increasing life expectancy, the demand for knee replacement has continuously risen over the past decades[1]. Despite the use of antibiotic prophylaxis and improved aseptic surgical techniques, periprosthetic joint infection (PJI) still occurs in 1% to 5% of patients who undergo primary arthroplasty[2,3]. Adequate treatment of PJI is mandatory to achieve a successful, infection-free outcome[4,5]. Commonly, patients undergo 1-, 2-, or multiple-stage revision surgery, depending on individual risk factors and pathogen characteristics[6]. Cemented prostheses are often chosen for reimplantation because of the possibility of additional local antibiotic therapy[7]. The surgical procedure comprises removal of the prosthesis affected by infection, debridement and irrigation, and, in a second-stage surgery, reimplantation of a new prosthesis into the cleaned bone bed[6]. Long-term survival of the new prosthesis depends on an adequate bone-cement interface with close interdigitating between cement and spongy bone[8]. However, mandatory septic debridement and removal of the infection-related prosthesis can lead to a reduction in bone mass and damage the femoral and tibial medullary cavities[9]. Previous research on long-term complications of PJI focused on septic complications and found an elevated risk of recurrent PJI of 5% to 15%[10]. An open question is the influence of PJI and the resulting surgical procedures on the occurrence of long-term complications such as aseptic loosening. Patients needing multiple revision surgeries are especially at risk for decreases in

Disclosure: The authors indicated that no external funding was received for any aspect of this work. The **Disclosure of Potential Conflicts of Interest** forms are provided with the online version of the article (http://links.lww.com/JBJSOA/A196).

JBJS Open Access • 2020:e20.00026. openaccess.jbjs.org

bone mass and damage to the medullary cavity[9]. We theorized that prior surgeries on the affected knee for any reason increase the risk of aseptic loosening in patients with PJI.

Preoperative risk factors can be screened for using clinical scoring systems such as the American Society of Anesthesiologists (ASA) classification and the Charlson Comorbidity Index (CCI). Both have been shown to correlate with postoperative complication and mortality rates for various conditions[11]. However, previous research focused either on the association with short-term complications or on long-term complications after primary knee arthroplasty[12,13]. It remains unclear whether ASA classification and CCI can be used as predictors of prosthetic survival in revision arthroplasty.

In this study, we retrospectively analyzed the cases of 100 patients who underwent cemented revision arthroplasty due to PJI to assess the prevalence of aseptic loosening and recurrent PJI and to analyze the utility of ASA classification and CCI in identifying patients with an increased risk of prosthetic failure.

Materials and Methods

Patients

This study was approved by the local ethics board and was performed in accordance with the Declaration of Helsinki. We retrospectively analyzed the cases of all patients who had undergone total knee replacement exchange surgery due to chronic PJI between January 2012 and January 2018. As a supra-regional university medical center, we often get complicated cases with prior PJI referred to our department. Cases involving PJI after primary and revision arthroplasty were included in this study. Patients were treated in our specialized department using a centralized and interdisciplinary treatment approach. In total, we analyzed the cases of 100 patients. Inclusion criteria were a previously implanted total knee replacement and diagnosed PJI that was successfully treated at the time of discharge. PJI was defined according to the European Bone and Joint Infection Society (EBJIS) criteria[14]: (1) prevalence of a sinus tract or purulence around a component; (2) >2,000 leukocytes/μL or >70% granulocytes in the synovial fluid; (3) histological confirmation of intraoperatively obtained tissue classified as Krenn and Morawietz type II or III[15]; or (4) microbiological growth in synovial fluid, ≥2 tissue samples (highly virulent organisms or in patients being treated with antibiotics: 1 positive sample), or sonication fluid (>50 colony-forming units per mL). Successful treatment at discharge was defined using modified Delphi criteria[16]: (1) wound-healing without fistula, drainage, pain, or recurrent infection; and (2) without PJI-related death due to sepsis.

Patients who met ≥1 of the following criteria were excluded from this study: (1) treatment with debridement, antibiotics, and implant retention (DAIR) or non-temporary arthrodesis; (2) no implantation of subsequent components after implant removal; (3) primary knee replacement due to infection; (4) primary knee replacement or reimplantation due to trauma without any pretraumatic signs of aseptic loosening; (5) incomplete postoperative clinical or radiographic examination; or (6) <6 months of postoperative follow-up. There were no further exclusions.

In addition to clinical, paraclinical, and radiographic parameters, we assessed comorbidities and the number of prior surgeries on the affected knee. Patient comorbidity was assessed using preoperative ASA classification[11] and age-adjusted CCI[17].

Surgical Technique

Two- or multiple-stage exchange surgery is widely accepted as standard treatment for PJI and was performed as previously described[6,18]. Briefly, after removal of the affected prosthesis, thorough debridement, and irrigation, patients received a temporary, antibiotic-loaded cement spacer between stages[19,20]. Reimplantation of a modular or nonmodular, cemented, rotating-hinge prosthesis was performed at least 6 weeks after removal when no clinical or paraclinical signs of infection were found. The vast majority (95%) of patients received a stemmed rotating-hinge or full-hinged prothesis. In detail, the Endo-Model (LINK) stemmed rotating-hinge prothesis was used in 55 cases, the RT-PLUS (Smith & Nephew) stemmed rotating-hinge prothesis was used in 32 cases, the Enduro (Aesculap) stemmed rotating-hinge prothesis was used in 1 case, and the Endo-Model (LINK) stemmed full-hinged prothesis was used in 7 cases. In the remaining 5 cases, the TC3 stemmed condylar constrained knee (CCK)-type prosthesis (DePuy Synthes, Johnson & Johnson) was used. All surgeries were performed by high-volume surgeons specializing in the treatment of PJI and revision total knee arthroplasty. Patients received antimicrobial therapy for up to 6 weeks after reimplantation[6]. Antimicrobial agents were chosen on the basis of bacterial susceptibility and the recommendations of Zimmerli et al.[21] and in consultation with our microbiologists.

Radiographic Analysis

Radiographic parameters were assessed to determine implant positioning using standing long-leg radiographs and anteroposterior and true lateral (30° of flexion) radiographs of the affected knee. Centricity Enterprise Web (v8.0.1400.511; GE Healthcare) was used for all measurements. Aseptic loosening was determined radiographically by assessing circumferential radiolucency at the bone-cement interface surrounding the prosthesis stem completely, prosthetic subsidence, change in the position of the stem or cement, or fractures in the cement mantle[22,23]. The diagnosis of aseptic loosening was dependent on radiographic criteria and patient-reported clinical symptoms of pain and instability.

Follow-up

To screen for complications after revision arthroplasty, we regularly invited patients to our outpatient department. Within the first postoperative year, patients were invited for radiographic and clinical follow-up every 3 months. After 1 year, the follow-up was offered annually. Besides aseptic loosening and recurrent PJI, complications of revision arthroplasty include, among others, instability, pain, patellar

JBJS Open Access • 2020:e20.00026.

TABLE I Patient Characteristics (N = 100)

	No. (%) of Patients	Mean (Range)
Descriptive		
Age *(yr)*		68.6 (34.0-85.1)
Male	46 (46.0)	
Female	54 (54.0)	
Right knee	54 (54.0)	
Left knee	46 (46.0)	
>1 comorbidity	95 (95.0)	
Clinical characteristics		
Body mass index *(kg/m²)*		31.0 (20.0-54.2)
CCI		3.7 (0-14)
ASA classification		
1	6 (6.0)	
2	43 (43.0)	
3	51 (51.0)	

maltracking, arthrofibrosis, and limited range of motion. For this study, prosthetic survival was defined as the absence of aseptic loosening and recurrent PJI. Prosthetic loosening was diagnosed using radiographic examination, as described above, while taking into account clinical symptoms. Recurrent PJI was diagnosed using EBJIS and modified Delphi criteria[14,16].

Statistics

Data were analyzed using Excel (version 16.30; Microsoft). Survival curves were used to plot prosthetic survival. All data are presented as the mean or the median with the range. Statistical analysis was performed using 1-way analysis of variance. An unpaired Student t test for samples of unequal variances was used to calculate significance ($p < 0.05$).

Results

Patients

Patient characteristics are outlined in Table I. Of the 100 patients included in our analysis, 46 were male and 54 were female. The median duration of follow-up was 37 months (range, 6 to 88 months). While 21 patients had experienced at least 1 PJI prior to PJI treatment at our clinic in the analyzed time frame, 70 patients were being treated for their first PJI. For 9 patients, the occurrence of a previous PJI was unknown. The mean body mass index (BMI) was 31.0 kg/m^2 (range, 20.0 to 54.2 kg/m^2). Ninety-five percent of the 100 patients had >1 comorbidity. The average CCI was 3.7 (range, 0 to 14). *Staphylococcus epidermidis, S. aureus,* and *Cutibacterium acnes* were the most common pathogens, comprising 60.0% of all cases. Pathogens found for all patients and each prosthesis-outcome group are shown in Table II. We found no significant differences among the prosthesis-outcome groups in terms of the pathogens identified.

Eighty-five patients underwent 2-stage exchange surgery, and 15 patients underwent multiple-stage exchange surgery.

Prevalence of Postoperative Aseptic Loosening and Recurrent PJI

While prosthetic survival was 98.0% at year 1, it dropped to 74.0% within 5 years and to 62.0% within 7.3 years after revision arthroplasty (Fig. 1-A). Sixteen percent of all patients had at least 1 more PJI in the 7.3 years of follow-up (Fig. 1-B); approximately half of those patients were infected with the same pathogen as before. For the first 5 years, recurrent PJI showed slightly higher occurrences, but thereafter, aseptic loosening was the more common complication (Fig. 1-B). Strikingly, 22.0% of all patients were diagnosed with aseptic loosening within 7.3 years of follow-up.

We observed a statistical trend of women being more at risk of developing aseptic loosening: 27.8% of all female patients had aseptic loosening compared with 15.2% of all male patients.

TABLE II Pathogens Found in Patients at Time of PJI

	All Patients (N = 100)		Prosthetic Survival (N = 62)		Aseptic Loosening (N = 22)			Recurrent PJI (N = 16)		
Descriptive	No.	%	No.	%	No.	%	P Value	No.	%	P Value
Coagulase-negative Staphylococci	54	54.0	37	59.7	11	50.0	0.879	6	37.5	0.259
Staphylococcus aureus	16	16.0	9	14.5	2	9.1	0.659	5	31.3	0.175
Cutibacterium acnes	15	15.0	10	16.1	2	9.1	0.559	3	18.8	0.851
Streptococci	6	6.0	3	4.8	0	0.0	0.332	3	18.8	0.080
Gram-negative bacteria	3	3.0	2	3.2	1	4.5	0.700	0	0.0	0.467
Other	16	16.0	11	17.7	4	18.2	0.798	1	6.3	0.283
None	21	21.0	11	17.7	6	27.3	0.268	4	25.0	0.587
Monomicrobial	58	58.0	35	56.5	14	63.6	0.705	9	56.3	0.992
Polymicrobial	21	21.0	16	25.8	2	9.1	0.146	3	18.8	0.610
Culture-negative	21	21.0	11	17.7	6	27.3	0.393	4	25.0	0.555

JBJS Open Access • 2020:e20.00026. **openaccess.jbjs.org** 4

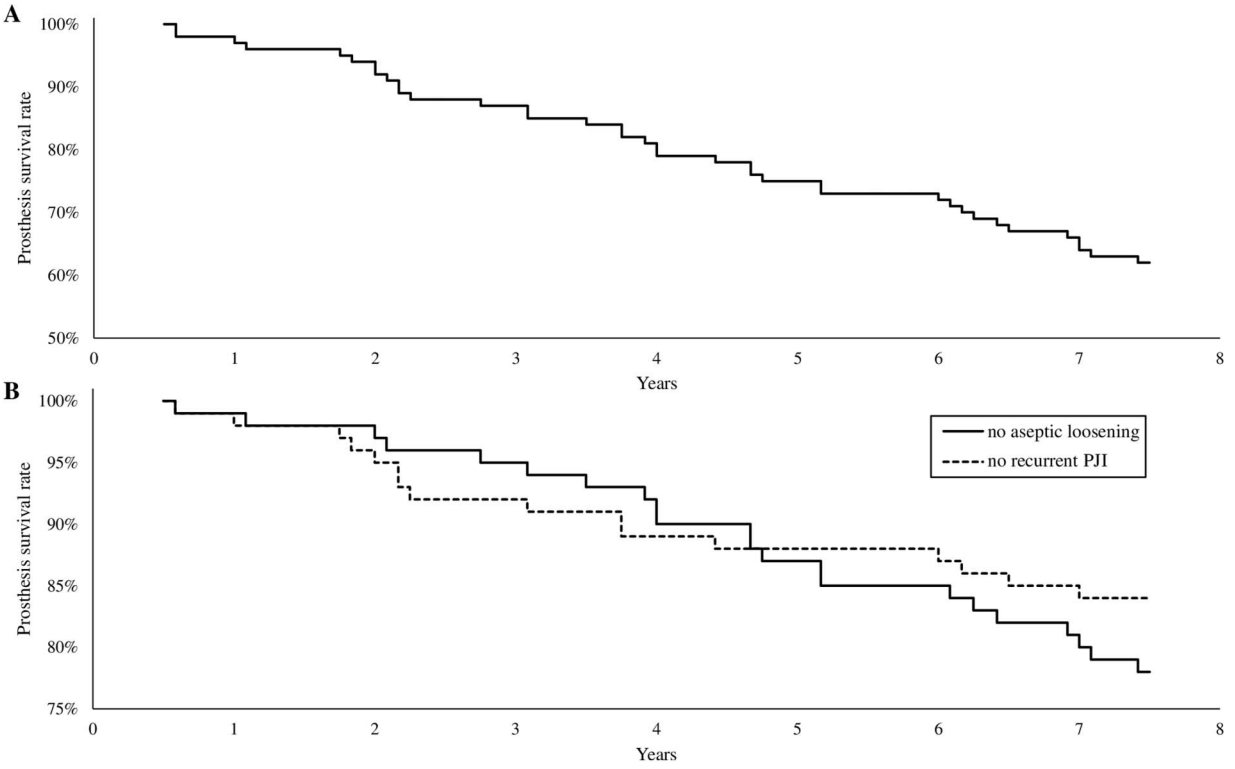

Fig. 1

Figs. 1-A and 1-B Prosthetic survival rates. **Fig. 1-A** Diagnosed recurrent PJI or aseptic loosening was considered failure of the prosthesis. While only 2.0% of all patients had failure of the prosthesis at year 1, the failure rate was drastically elevated to 26.0% within 5 years. Prosthetic survival continued to decline until the end of our study and was 62.0% at 7.3 years. **Fig. 1-B** Comparison of prosthetic failure due to recurrent PJI (dashed line) and aseptic loosening (solid line). In the first 5 years, the prevalence of recurrent PJI was higher than the prevalence of aseptic loosening. At 7.3 years, 16.0% of all patients had experienced recurrent PJI. In comparison, 22.0% were diagnosed with aseptic loosening.

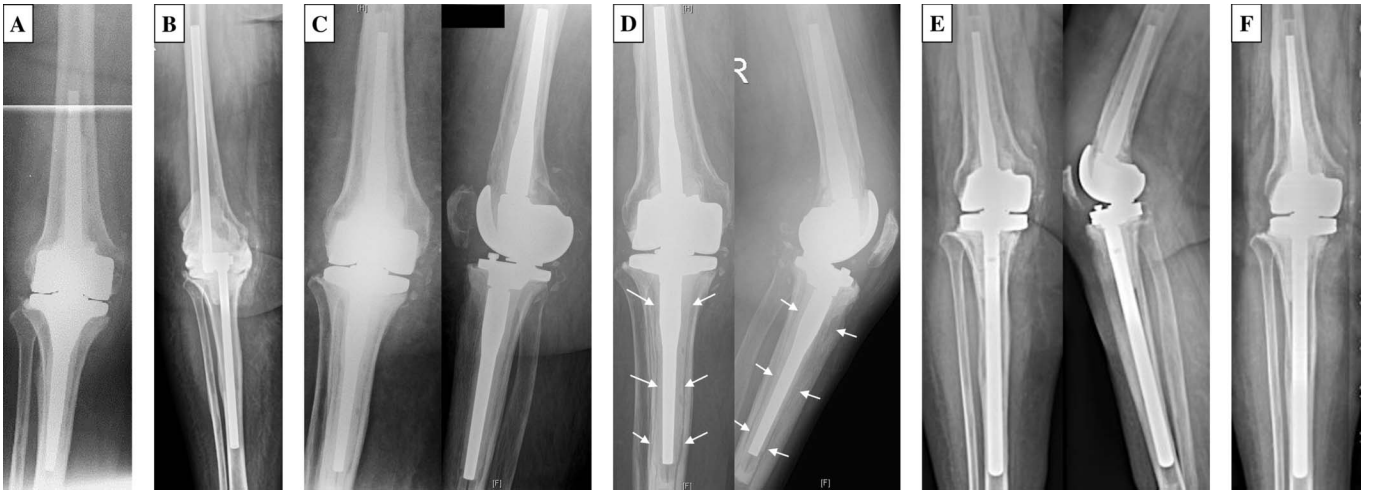

Fig. 2

Figs. 2-A through 2-F Images of a 63-year-old patient who had recurrent PJI with multiple revision surgeries. **Fig. 2-A** The patient experienced recurrent PJI after having received a hinged knee prosthesis during revision arthroplasty due to PJI 2 years prior. **Fig. 2-B** First-stage revision arthroplasty: prosthesis removal and temporal arthrodesis using a spacer and antibiotic-loaded cement. **Fig. 2-C** Second-stage revision arthroplasty: reimplantation of a hinged knee prosthesis 6 weeks later. **Fig. 2-D** Clinical and radiographic signs of aseptic loosening (arrows) of the tibial component after 2 years. **Fig. 2-E** After clinical, pathological, and microbiological exclusion of infection, the patient's tibial component was changed to a cementless prosthesis. **Fig. 2-F** Good clinical, functional, and radiographic outcomes in the 1-year follow-up examination.

JBJS Open Access • 2020:e20.00026. **openaccess.jbjs.org** 5

Figure 2 shows images of a representative patient who experienced aseptic loosening after multiple revision procedures with cemented components. In this case, after clinical, pathological, and microbiological exclusion of infection, the patient's tibial component was changed to a cementless prosthesis.

Clinical Scores

The prevalence of aseptic and septic long-term complications was significantly increased among patients with higher preoperative ASA classification ($p = 0.020$) (Fig. 3). While no patient classified as ASA 1 had aseptic loosening, 1 patient in that group had recurrent PJI. Of the 43 patients classified as ASA 2, six patients had aseptic loosening and 4 had recurrent PJI. The prevalence of long-term complications was highest in the group classified as ASA 3. In contrast, CCI correlated only moderately with the prevalence of aseptic loosening ($r = 0.40$) and recurrent PJI ($r = 0.44$).

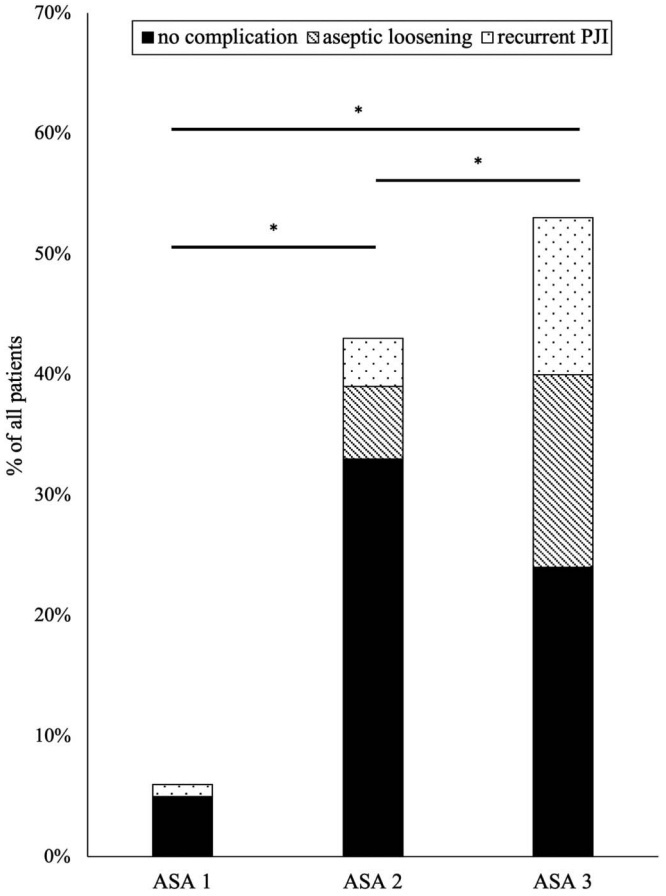

Fig. 3

Association between prosthetic failure rate and ASA score. Most patients were scored as ASA 2 or 3. While only 1 patient classified as ASA 1 had recurrent PJI, 6.0% of all patients had aseptic loosening and 4.0% had recurrent PJI in the ASA 2 group. The prevalence of long-term complications was highest in the ASA 3 group: 16.0% and 13.0% of all patients were diagnosed with aseptic loosening or recurrent PJI, respectively. *Significant difference among the groups ($p < 0.05$).

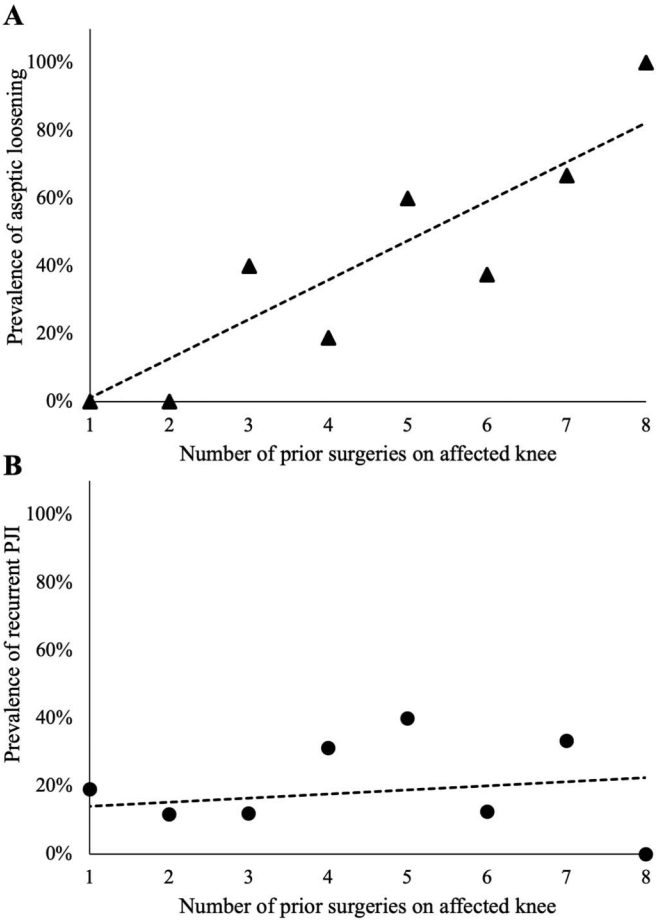

Fig. 4

Figs. 4-A and 4-B Correlations of the prevalence of aseptic loosening and recurrent PJI with number of prior surgeries. **Fig. 4-A** Prevalence of aseptic loosening correlated strongly ($r = 0.91$) with number of prior surgeries on the affected knee. **Fig. 4-B** Prevalence of recurrent PJI did not correlate ($r = 0.23$) with number of prior surgeries. The linear trend line is shown as a dashed line.

Preoperative Knee Surgery

To assess the impact of the number of surgeries on the affected knee and prosthetic survival, we evaluated the correlation between prevalence of aseptic and septic complications and number of prior surgeries. Prevalence of aseptic loosening significantly ($p = 0.008$) and strongly ($r = 0.91$) correlated with number of prior surgeries (Fig. 4-A). In contrast, no correlation ($r = 0.23$) was found between number of prior surgeries and recurrent PJI (Fig. 4-B).

The prevalence of aseptic loosening and recurrent PJI was 17.1% and 15.7%, respectively, for patients with no prior PJI. In the subgroup of patients with prior PJI, the prevalence of aseptic loosening was further elevated to 38.1%, while the prevalence of recurrent PJI was 19.0%.

Discussion

In this study, we used clinical, paraclinical, and radiographic examinations to study the prevalence of the long-term

complications aseptic loosening and recurrent PJI among patients with prior PJI who had undergone subsequent revision surgery. Additionally, we retrospectively analyzed the utility of ASA classification and CCI to identify patients with an increased risk of prosthetic failure. The long-term arthroplasty failure rate was drastically elevated after revision surgery due to PJI.

Strikingly, we found that the prosthetic failure rate after PJI-related revision surgery was 22.0% for aseptic loosening in the first 7.3 years after revision surgery. In contrast, the prevalence of aseptic loosening in the first 6.5 years after primary arthroplasty previously was found to be 1% to 5%[24]. Similar to our results, Suarez et al. reported a prevalence of 19% for aseptic loosening after indication-independent revision knee arthroplasty[25]. An open question is the role of surgical techniques and the impact of PJI on the bone metabolism in the development of aseptic loosening.

Previous studies suggested that the occurrence of aseptic loosening hinges on the biological properties of the bone[26]. Wear particles from cement, metal, and polyethylene play a decisive role in the development of aseptic loosening by impacting the bone metabolism[27,28]. While PJI leads to an inflammatory response[29], the effects of PJI on postoperative bone metabolism remain largely unclear. The observed differences in the prevalence of aseptic loosening between male and female patients supports theories surrounding the role of bone metabolism in the development of aseptic loosening, as sex-specific differences in bone metabolism have been demonstrated previously[30]. The economic and clinical burden makes it paramount to gain a better understanding of bone metabolism in PJI.

Additionally, we demonstrated that ASA classification was associated with the prevalence of aseptic loosening and recurrent PJI. Similar to our findings, previous studies postulating a correlation of ASA scores with bone metabolism and clinical outcome demonstrated increased short and long-term complications after primary arthroplasty[31,32]. However, we found only a moderate correlation between CCI and the development of aseptic loosening and recurrent PJI. Strong discrepancies between CCI and ASA scores have been described previously and may explain the differences in the strengths of their predictive values found in our study[33].

There is an obvious need to optimize treatment strategies to increase prosthetic survival. Currently, the use of antibiotic-loaded cement and 1-, 2-, or multiple-stage revision surgery is recommended. PJI-related revision arthroplasty consists of the removal of the infected prosthesis, debridement, irrigation, and reimplantation of a new prosthesis into the cleaned bone bed[6]. In cases in which multiple revisions are needed, every subsequent surgery decreases remaining bone mass[9], thus reducing the spongy bone surface area needed for cement penetration and successful long-term fixation. Our data indicate a correlation between long-term prosthetic failure due to aseptic loosening and the number of prior surgeries, including prior PJI revision surgery. An adequate bone-cement interface with interdigitation between cement and spongy bone is mandatory for prosthetic survival[8]. To avoid a loss of bone mass with every revision surgery, arthroplasty with cementless components could offer a way forward in complicated cases[34]. In patients with little remaining cancellous bone due to multiple revision surgeries, cementless prostheses can be anchored in the cortical bone[35]. Complication and prosthetic survival rates were found to be significantly improved for patients receiving cementless arthroplasty for lower limb salvage surgery[36]. Additionally, a review comparing cementless and cemented fixation in primary arthroplasty found no significant differences in long-term outcomes[37]. However, it has yet to be debated whether the absence of antibiotic-loaded cement may increase the risk of recurrent PJI. Antimicrobial nanoparticle prosthetic coatings might offer a suitable alternative[38-41]. Furthermore, because longer stems are needed for cementless prostheses, the intraoperative risk of periprosthetic fractures and the rates of perforation of the tibia or femur are increased[42,43]. Additionally, increased shear forces caused by longer stems and a high level of constraint should be discussed as a plausible mechanism leading to aseptic loosening. In support of this theory, almost all patients in our study received implants with a high level of constraint. On the basis of our results, implants with the least possible levels of constraint may be preferable for septic revision arthroplasty. In contrast, Hossain et al. reported midterm satisfaction to be highest among patients who received rotating-hinge implants in revision arthroplasty[44]. In cases involving extended bone loss, cones and sleeves allowing stable metaphyseal prosthetic fixation can reduce shear forces and thus potentially decrease prosthetic failure rates[45]. Additional research is needed to address the impact of the prosthetic design on post-revision prosthetic failure and to evaluate whether revision arthroplasty with cementless or non-constrained implants can be deemed a preferred treatment strategy.

Limitations of the current study include the heterogeneity of the analyzed population, differences in the type of revision implant used, and the short follow-up duration in a few cases. Although longer minimum follow-up for recurrent PJI is generally agreed upon, we chose a minimum follow-up duration of 6 months to ensure that we did not miss any patients with early signs of aseptic loosening. While too-short minimum follow-up times might skew the data toward lower prosthetic failure rates, exclusion of these patients overstates these rates. An additional limitation is that, in some cases, partial prosthetic loosening can be difficult to diagnose. Previous reports suggested that the number of affected patients is higher than originally assumed[46]. Conversely, it has been suggested that, in some patients, loosening is in fact not aseptic but due to occult infection[47,48]. Both factors potentially influence prosthetic failure rates presented in our study.

In this study, 16% of all patients had recurrent PJI in the first 7.3 years after revision arthroplasty. After primary arthroplasty, the risk of PJI has been reported to be only 1% to 5%[2,3,49]. In accordance with our results, previous research on septic long-term complications found an increased risk of recurrent PJI of 5% to 15%[10,49]. In approximately half of the cases with recurrent PJI, the pathogen found was the same as that previously diagnosed for the initial PJI. The role of incomplete pathogen elimination in such cases is the subject of ongoing debate[50]. In cases with different pathogens in the sense of a new infection, PJI recurrence may happen intraoperatively during revision surgery

or may be hematogenous[51]. It is unknown whether changes in the vascularization of the soft tissue surrounding the knee potentially compromise effective immune system responses. The regenerative capacities of various tissues have been linked to local immune system activity[52,53]. Conversely, in the current study, no correlation between the number of prior surgeries and the prevalence of recurrent PJI was found. As prior surgeries also include those performed for reasons other than infection, it can be speculated that PJI-related inflammation has a substantial impact on the bone and soft tissue of the knee.

In conclusion, the prevalence of aseptic loosening and recurrent PJI was drastically elevated in patients after PJI-related revision arthroplasty: within 7.3 years of follow-up, 22.0% of all patients had aseptic loosening and 16.0% had recurrent PJI. ■

NOTE: The authors thank Josh O. Rose for critical proofreading of the manuscript.

Arne Kienzle, MD[1,2]
Sandy Walter[1]
Philipp von Roth, MD[3]
Michael Fuchs, MD[4]
Tobias Winkler, MD[1]
Michael Müller, MD[1]

[1]Center for Musculoskeletal Surgery, Clinic for Orthopedics and Traumatology, Charité University Hospital Berlin, Berlin, Germany

[2]Laboratory of Adaptive and Regenerative Biology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts

[3]Sporthopaedicum, Straubing, Germany

[4]RKU University Department of Orthopedics, University of Ulm, Ulm, Germany

Email address for A. Kienzle: arne.kienzle@charite.de

ORCID iD for A. Kienzle: 0000-0002-4556-2993
ORCID iD for S. Walter: 0000-0002-0958-1038
ORCID iD for P. von Roth: 0000-0002-6724-9279
ORCID iD for M. Fuchs: 0000-0002-5557-682X
ORCID iD for T. Winkler: 0000-0003-0727-4680
ORCID iD for M. Müller: 0000-0002-8934-9676

References

1. Kurtz SM, Ong KL, Schmier J, Mowat F, Saleh K, Dybvik E, Kärrholm J, Garellick G, Havelin LI, Furnes O, Malchau H, Lau E. Future clinical and economic impact of revision total hip and knee arthroplasty. J Bone Joint Surg Am. 2007 Oct;89(Suppl 3):144-51.

2. Delanois RE, Mistry JB, Gwam CU, Mohamed NS, Choksi US, Mont MA. Current epidemiology of revision total knee arthroplasty in the United States. J Arthroplasty. 2017 Sep;32(9):2663-8. Epub 2017 Apr 6.

3. Kurtz SM, Lau E, Schmier J, Ong KL, Zhao K, Parvizi J. Infection burden for hip and knee arthroplasty in the United States. J Arthroplasty. 2008zOct;23(7):984-91. Epub 2008 Apr 10.

4. Insall JN, Thompson FM, Brause BD. Two-stage reimplantation for the salvage of infected total knee arthroplasty. J Bone Joint Surg Am. 1983 Oct;65(8): 1087-98.

5. Poss R, Thornhill TS, Ewald FC, Thomas WH, Batte NJ, Sledge CB. Factors influencing the incidence and outcome of infection following total joint arthroplasty. Clin Orthop Relat Res. 1984 Jan-Feb;182:117-26.

6. Karczewski D, Winkler T, Renz N, Trampuz A, Lieb E, Perka C, Müller M. A standardized interdisciplinary algorithm for the treatment of prosthetic joint infections. Bone Joint J. 2019 Feb;101-B(2):132-9.

7. Jiranek WA, Hanssen AD, Greenwald AS. Antibiotic-loaded bone cement for infection prophylaxis in total joint replacement. J Bone Joint Surg Am. 2006 Nov; 88(11):2487-500.

8. Johanson NA, Bullough PG, Wilson PD Jr, Salvati EA, Ranawat CS. The microscopic anatomy of the bone-cement interface in failed total hip arthroplasties. Clin Orthop Relat Res. 1987 May;218:123-35.

9. Calton TF, Fehring TK, Griffin WL. Bone loss associated with the use of spacer blocks in infected total knee arthroplasty. Clin Orthop Relat Res. 1997 Dec;345: 148-54.

10. Urquhart DM, Hanna FS, Brennan SL, Wluka AE, Leder K, Cameron PA, Graves SE, Cicuttini FM. Incidence and risk factors for deep surgical site infection after primary total hip arthroplasty: a systematic review. J Arthroplasty. 2010 Dec;25(8): 1216-22.e1:3. Epub 2009 Oct 30.

11. Wolters U, Wolf T, Stützer H, Schröder T. ASA classification and perioperative variables as predictors of postoperative outcome. Br J Anaesth. 1996 Aug;77(2): 217-22.

12. Jämsen E, Varonen M, Huhtala H, Lehto MU, Lumio J, Konttinen YT, Moilanen T. Incidence of prosthetic joint infections after primary knee arthroplasty. J Arthroplasty. 2010 Jan;25(1):87-92. Epub 2008 Dec 4.

13. Deleuran T, Vilstrup H, Overgaard S, Jepsen P. Cirrhosis patients have increased risk of complications after hip or knee arthroplasty. Acta Orthop. 2015 Feb;86(1):108-13. Epub 2014 Sep 19.

14. Ochsner PE, Borens O, Bodler PM. Schweizerische Gesellschaft für Orthopädie und Traumatologie. Infections of the musculoskeletal system: basic principles, prevention, diagnosis and treatment. Swiss Orthopaedics In-House Publisher; 2014.

15. Krenn V, Morawietz L, Perino G, Kienapfel H, Ascherl R, Hassenpflug GJ, Thomsen M, Thomas P, Huber M, Kendoff D, Baumhoer D, Krukemeyer MG, Natu S, Boettner F, Zustin J, Kölbel B, Rüther W, Kretzer JP, Tiemann A, Trampuz A, Frommelt L, Tichilow R, Söder S, Müller S, Parvizi J, Illgner U, Gehrke T. Revised histopathological consensus classification of joint implant related pathology. Pathol Res Pract. 2014 Dec;210(12):779-86. Epub 2014 Oct 17.

16. Diaz-Ledezma C, Higuera CA, Parvizi J. Success after treatment of periprosthetic joint infection: a Delphi-based international multidisciplinary consensus. Clin Orthop Relat Res. 2013 Jul;471(7):2374-82. Epub 2013 Feb 26.

17. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-83.

18. Zimmerli W, Moser C. Pathogenesis and treatment concepts of orthopaedic biofilm infections. FEMS Immunol Med Microbiol. 2012 Jul;65(2):158-68. Epub 2012 Mar 15.

19. Röhner E, Pfitzner T, Preininger B, Zippelius T, Perka C. Temporary arthrodesis using fixator rods in two-stage revision of septic knee prothesis with severe bone and tissue defects. Knee Surg Sports Traumatol Arthrosc. 2016 Jan;24(1):84-8. Epub 2014 Sep 24.

20. Masri BA, Duncan CP, Beauchamp CP. Long-term elution of antibiotics from bone-cement: an in vivo study using the prosthesis of antibiotic-loaded acrylic cement (PROSTALAC) system. J Arthroplasty. 1998 Apr;13(3):331-8.

21. Zimmerli W, Trampuz A, Ochsner PE. Prosthetic-joint infections. N Engl J Med. 2004 Oct 14;351(16):1645-54.

22. Ewald FC. The Knee Society total knee arthroplasty roentgenographic evaluation and scoring system. Clin Orthop Relat Res. 1989 Nov;248:9-12.

23. Gonzalez MH, Mekhail AO. The failed total knee arthroplasty: evaluation and etiology. J Am Acad Orthop Surg. 2004 Nov-Dec;12(6):436-46.

24. Thiele K, Perka C, Matziolis G, Mayr HO, Sostheim M, Hube R. Current failure mechanisms after knee arthroplasty have changed: polyethylene wear is less common in revision surgery. J Bone Joint Surg Am. 2015 May 6;97(9):715-20.

25. Suarez J, Griffin W, Springer B, Fehring T, Mason JB, Odum S. Why do revision knee arthroplasties fail? J Arthroplasty. 2008 Sep;23(6)(Suppl 1):99-103. Epub 2008 Jun 5.

26. Schmalzried TP, Kwong LM, Jasty M, Sedlacek RC, Haire TC, O'Connor DO, Bragdon CR, Kabo JM, Malcolm AJ, Harris WH. The mechanism of loosening of cemented acetabular components in total hip arthroplasty. Analysis of specimens retrieved at autopsy. Clin Orthop Relat Res. 1992 Jan;274:60-78.

27. Howie DW, Vernon-Roberts B, Oakeshott R, Manthey B. A rat model of resorption of bone at the cement-bone interface in the presence of polyethylene wear particles. J Bone Joint Surg Am. 1988 Feb;70(2):257-63.

28. Mirra JM, Marder RA, Amstutz HC. The pathology of failed total joint arthroplasty. Clin Orthop Relat Res. 1982 Oct;170:175-83.

29. Song Z, Borgwardt L, Høiby N, Wu H, Sørensen TS, Borgwardt A. Prosthesis infections after orthopedic joint replacement: the possible role of bacterial biofilms. Orthop Rev (Pavia). 2013 Jun 14;5(2):65-71.

30. Henry YM, Eastell R. Ethnic and gender differences in bone mineral density and bone turnover in young adults: effect of bone size. Osteoporos Int. 2000;11(6):512-7.

31. Schaeffer JF, Scott DJ, Godin JA, Attarian DE, Wellman SS, Mather RC 3rd. The association of ASA class on total knee and total hip arthroplasty readmission rates in an academic hospital. J Arthroplasty. 2015 May;30(5):723-7. Epub 2014 Dec 16.

32. Hooper GJ, Rothwell AG, Hooper NM, Frampton C. The relationship between the American Society of Anesthesiologists physical rating and outcome following total hip and knee arthroplasty: an analysis of the New Zealand Joint Registry. J Bone Joint Surg Am. 2012 Jun 20;94(12):1065-70.

33. Bjorgul K, Novicoff WM, Saleh KJ. Evaluating comorbidities in total hip and knee arthroplasty: available instruments. J Orthop Traumatol. 2010 Dec;11(4):203-9. Epub 2010 Nov 13.

34. Edwards PK, Fehring TK, Hamilton WG, Perricelli B, Beaver WB, Odum SM. Are cementless stems more durable than cemented stems in two-stage revisions of infected total knee arthroplasties? Clin Orthop Relat Res. 2014 Jan;472(1):206-11.

35. Abu-Rajab RB, Watson WS, Walker B, Roberts J, Gallacher SJ, Meek RM. Periprosthetic bone mineral density after total knee arthroplasty. Cemented versus cementless fixation. J Bone Joint Surg Br. 2006 May;88(5):606-13.

36. Pala E, Mavrogenis AF, Angelini A, Henderson ER, Douglas Letson G, Ruggieri P. Cemented versus cementless endoprostheses for lower limb salvage surgery. J BUON. 2013 Apr-Jun;18(2):496-503.

37. Matassi F, Carulli C, Civinini R, Innocenti M. Cemented versus cementless fixation in total knee arthroplasty. Joints. 2014 Jan 8;1(3):121-5.

38. He W, Liu X, Kienzle A, Müller WE, Feng Q. In vitro uptake of silver nanoparticles and their toxicity in human mesenchymal stem cells derived from bone marrow. J Nanosci Nanotechnol. 2016 Jan;16(1):219-28.

39. Liu X, He W, Fang Z, Kienzle A, Feng Q. Influence of silver nanoparticles on osteogenic differentiation of human mesenchymal stem cells. J Biomed Nanotechnol. 2014 Jul;10(7):1277-85.

40. He W, Kienzle A, Liu X, Müller WE, Elkhooly TA, Feng Q. In vitro effect of 30 nm silver nanoparticles on adipogenic differentiation of human mesenchymal stem cells. J Biomed Nanotechnol. 2016 Mar;12(3):525-35.

41. Kienzle A, Kurch S, Schlöder J, Berges C, Ose R, Schupp J, Tuettenberg A, Weiss H, Schultze J, Winzen S, Schinnerer M, Koynov K, Mezger M, Haass NK, Tremel W, Jonuleit H. Dendritic mesoporous silica nanoparticles for pH-stimuli-responsive drug delivery of TNF-alpha. Adv Healthc Mater. 2017 Jul;6(13). Epub 2017 May 29.

42. Foster AP, Thompson NW, Wong J, Charlwood AP. Periprosthetic femoral fractures—a comparison between cemented and uncemented hemiarthroplasties. Injury. 2005 Mar;36(3):424-9.

43. Toni A, Ciaroni D, Sudanese A, Femino F, Marraro MD, Bueno Lozano AL, Giunti A. Incidence of intraoperative femoral fracture. Straight-stemmed versus anatomic cementless total hip arthroplasty. Acta Orthop Belg. 1994;60(1):43-54.

44. Hossain F, Patel S, Haddad FS. Midterm assessment of causes and results of revision total knee arthroplasty. Clin Orthop Relat Res. 2010 May;468(5):1221-8.

45. Salim X, Lopez D, Jeys L, Carey Smith R. Cones and sleeves in knee arthroplasty: a narrative review. Curr Orthop Pract. 2019 Nov/Dec;30(6):520-5.

46. Abele JT, Swami VG, Russell G, Masson EC, Flemming JP. The accuracy of single photon emission computed tomography/computed tomography arthrography in evaluating aseptic loosening of hip and knee prostheses. J Arthroplasty. 2015 Sep;30(9):1647-51. Epub 2015 Mar 31.

47. Nelson CL, McLaren AC, McLaren SG, Johnson JW, Smeltzer MS. Is aseptic loosening truly aseptic? Clin Orthop Relat Res. 2005 Aug;437:25-30.

48. Kempthorne JT, Ailabouni R, Raniga S, Hammer D, Hooper G. Occult infection in aseptic joint loosening and the diagnostic role of implant sonication. BioMed Res Int. 2015;2015:946215. Epub 2015 Oct 25.

49. Blom AW, Brown J, Taylor AH, Pattison G, Whitehouse S, Bannister GC. Infection after total knee arthroplasty. J Bone Joint Surg Br. 2004 Jul;86(5):688-91.

50. Zmistowski B, Tetreault MW, Alijanipour P, Chen AF, Della Valle CJ, Parvizi J. Recurrent periprosthetic joint infection: persistent or new infection? J Arthroplasty. 2013 Oct;28(9):1486-9. Epub 2013 Apr 12.

51. Akgün D, Müller M, Perka C, Winkler T. An often-unrecognized entity as cause of recurrent infection after successfully treated two-stage exchange arthroplasty: hematogenous infection. Arch Orthop Trauma Surg. 2018 Sep;138(9):1199-206. Epub 2018 Jun 5.

52. Julier Z, Park AJ, Briquez PS, Martino MM. Promoting tissue regeneration by modulating the immune system. Acta Biomater. 2017 Apr 15;53:13-28. Epub 2017 Jan 22.

53. Kienzle A, Servais AB, Ysasi AB, Gibney BC, Valenzuela CD, Wagner WL, Ackermann M, Mentzer SJ. Free-floating mesothelial cells in pleural fluid after lung surgery. Front Med (Lausanne). 2018 Apr 5;5:89.