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Loosening of total knee arthroplasty – always aseptic?

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ABSTRACT

Purpose: When revision surgery is needed in total knee arthroplasty (TKA) the most frequent reasons are aseptic loosening (AL) and periprosthetic joint infection (PJI). However preoperative distinction between AL and PJI remains challenging. Aim of this study is to determine the incidence of PJI in patients with suspected AL after TKA and to evaluate a diagnostic algorithm for reliable differential diagnosis.
Methods: In this study a total of 149 symptomatic patients with radiographic signs of prosthetic loosening and suspected AL were included. Preoperatively all patients underwent a standardized diagnostic algorithm. For each patient demographics, as well as the results of laboratory and microbiological testing were collected from the medical records.
Results: Of the included patients 117 (78.5%) were diagnosed with AL and 32 (21.5%) with PJI. The latency period from primary arthroplasty to the presentation with symptomatic implant loosening was significantly shorter for PJI compared to AL ($p < 0.05$). The initial CRP values were significantly higher in patients with PJI compared to patients with AL ($p < 0.05$). Elevated count of white blood cells or percentage of neutrophils within the synovial fluid support the diagnosis of PJI. The sensitivity of synovial cell count (CC) count for PJI in patients with radiographic signs of loosening was 0.84 (CI 0.81–0.87) with a specificity of 0.96 (CI 0.92–0.98). The single best measure for the diagnosis of PJI was synovial fluid cultures with a specificity of 1, however this measure provides poor sensitivity.
Conclusion: Patients with radiographic signs of loosening in TKA need thorough diagnostics. Information about primary TKA, serological testing, and results of joint aspiration can rule out a PJI in most cases.

1. Introduction

Total knee arthroplasty (TKA) represents a successful procedure providing durable results for the majority of patients.[1,2] However, revision surgery after TKA still remains a common challenge.[3] In this context, the Australian Orthopaedic Association National Joint Replacement Registry reported increasing revisions rates in TKA with up to 8.3% of all knee replacement procedures.[4] Overall, the two most frequent reasons for revision surgery in TKA are aseptic loosening (AL) and periprosthetic joint infections (PJI).[3,4]

A Swedish study has shown that AL is the most frequent complication after TKA accounting for about 44% of total knee revisions.[5] However, the differentiation between AL and PJI remains challenging and, due to similar clinical symptoms and radiographic findings, a significant number of misdiagnosis is assumed.[6] In aseptic loosening a local inflammatory process with involvement of several cell types and cytokines activating osteoclasts leads to bone resorption.[7] However, bone resorption and loosening of the prosthesis can also be a consequence of an infection, usually caused by low virulent bacteria.[8] Similar to AL, infections with low virulent bacteria demonstrate moderate local pain and present with radiographic findings of loosening.[9] However, loosening is not a criterion of PJI that may also occur with stable implants.

Due to the consequences for further treatment, infection should always be ruled out in patients with symptomatic TKA and radiological signs of prosthesis loosening.[9] As a result of the complexity to achieve diagnostic certainty, the American Academy of Hip and Knee Surgeons presented a standardized approach for the diagnosis of PJI in 2017.[10] As a first step, patients with residual pain after TKA receive serologic testing (CRP), followed by joint fluid aspiration of the knee joint. Synovial cell count (CC), polymorphonuclear percentage (PMN%), and cultures are the evaluated within the joint

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fluid. This algorithm resembles the treatment algorithm assessed in this study. Parvizi et al.[11] offered an evidence-based definition for diagnosing knee PJI in 2018. The authors presented a validated criteria for diagnosing PJI.

Our hypothesis was that patients with radiographic signs of osteolysis around a TKA essentially need further diagnostics including serological testing in combination with joint aspiration to detect a PJI. Aim of the present study was to determine the characteristics and incidence of PJI in patients with radiographic signs of prosthetic loosening after TKA. We assumed a correlation between aseptic loosening and prosthesis-age.

2. Patients and methods

2.1. Study design

The local institutional review board approved this study. All patients undergoing revision TKA for prosthetic loosening between July 2012 and December 2016 were retrospectively included in this study. According to Vanrusselt et al.[12] diagnosis of implant loosening was made when periimplant lucency greater than 2 mm was present in the absence of local or systemic signs of infection. For each patient included in this study the following data was collected from the medical record: gender, age, body mass index (BMI), time between the primary arthroplasty and joint fluid aspiration, CRP (mg/dl) on the date of joint fluid aspiration, serum white blood cell (WBC) count on the date of joint fluid aspiration, results from synovial fluid analysis (CC, PMN %), results from the synovial fluid cultures, and microbiological analysis of the five intraoperative tissues. Preoperatively all patients underwent a standardized diagnostic algorithm as shown in Fig. 1.

According to the classification of the Musculoskeletal Infection Society (MSIS), PJI was assumed preoperatively when a sinus tract or other open communication between wound and involved joint was present or when three of the following four abnormalities were existing: elevated CRP (>1 mg/dl), synovial cell count (CC) greater than 3000 cells/µl, synovial polymorphonuclear percentage (>65%) or a bacterial growth from two synovial aspirate cultures.[13] Additionally, blood testing for WBC count was performed. Joint fluid aspiration was achieved under aseptic conditions in an operating room and incubated in aerobic and anaerobic blood culture bottles. 11 ml synovial fluid was necessary to run all the tests (1 ml CC, 5 ml aerobic, 5 ml anaerobic). In cases of negative joint fluid aspiration in combination with two positive other findings a repeat aspiration was performed one month later. All patients diagnosed with AL underwent a single-stage surgical revision in which all prosthetic components and the cement were removed, followed by debridement and a re-implantation of new and appropriate prosthetic components. Patients with PJI underwent a multi-stage surgical revision. After initial removal of all components an antibiotic-impregnated cement spacer (Vancomycin and Gentamycin) was positioned into the knee joint. All spacers were mobile spacers. A multidisciplinary antimicrobial treatment team of pharmacists and clinical microbiologists were involved in all cases for choosing antibiotics. After eradicating infection the final stage includes explantation of the cement spacer, removal of all cement fragments, thorough debridement and placement of the new appropriate prosthetic components. For retrospective validation of the results five periprosthetic soft tissue samples were obtained in all 149 cases during the initial revision surgery for microbiological analysis. The five prosthetic soft tissue samples were gathered seperately from five different locations of the surgical field and were graded as positive when at least two samples showed bacterial growth to rule out contamination. For statistical analysis between groups one-way ANOVA test followed by the post-hoc Dunn's test using SPSS software pack (version 23, IBM, New York, USA). P value < 0.05 was considered for statistic significance.

3. Results

A total of 149 patients with signs of loosening were included in this study. The mean age was 72.8 years (range 46–92 years). According to the criteria 117 (78.5%) patients were diagnosed with aseptic loosening and 32 (21.5%) patients with periprosthetic joint infection. 114 (97.4%) patients identified with aseptic loosening had negative cultures at intraoperative collection of five periprosthetic tissue specimens. No patient in the study cohort presented with any of the major MSIS criteria (sinus tract or other open communication between wound and involved joint). In three patients (2.6%) one of the five intraoperatively harvested tissue samples was

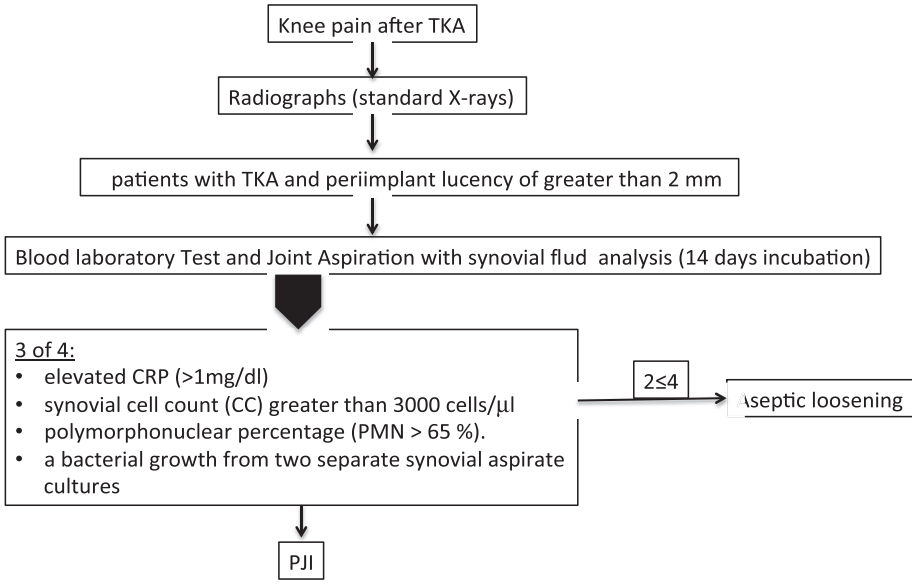

Fig. 1. Diagnostic protocol.

positive for microorganism, even though in these cases all preoperatively applied measures for the detection of an infection were negative. According to the criteria described above these positive cultures were rated as contamination. All 32 Patients diagnosed preoperatively with PJI had 2 or more intraoperative soft tissue samples positive for microorganisms.

Patients diagnosed with PJI had a significantly shorter time between primary arthroplasty and joint aspiration compared to AL ($p < 0.05$). The latency period between primary total knee arthroplasty and joint fluid aspiration is shown in Fig. 2.

CRP values at the date of joint fluid aspiration were significantly higher in the PJI group compared to AL group ($p < 0.05$), however no significant differences were seen in WBC count in the blood ($p > 0.05$)

Of the 32 patients with PJI 84% ($n = 27$) presented with CRP values greater than 1 mg/dl, whereas 22.2% ($n = 26$) of the 117 patients with AL showed CRP values greater than 1 mg/dl on the date of joint fluid aspiration (Table 2). Synovial fluid results for both groups are shown in Table 3. Patients with PJI had significantly ($p < 0.05$) higher synovial cell counts (CC) and significantly ($p < 0.05$) higher synovial polymorphonuclear percentage (PMN %).

Of all patients with PJI 20 patients (62.5%) were positive for CRP, synovial cell count, polymorphonuclear percentage, and synovial culture. The remaining 12 patients (37.5%) presented with a combination of three of these four criteria. In nine patients the synovial culture of two joint aspirations was negative, however a combination of elevated CRP, elevated CC, and elevated (PMN) was present. Of the 117 patients diagnosed with AL 36 (30.8%) showed one of the following diagnostic criteria alone: 26 (22.2%) with elevated CRP, four (3.4%) with elevated CCm in joint fluid aspirate, six (5.1%) with elevated PMN. In none of the 117 patients diagnosed with AL bacterial growth was detected in synovial fluid cultures. The sensitivity and specificity is shown in Table 4.

4. Discussion

Critical Evaluation of patients with painful dysfunction of a TKA is complex. The most commonly used diagnostic modalities include radiographs and serological testing. Is this enough for sufficient differential diagnosis? Aseptic loosening and periprosthetic joint infection are the most common failure modes following total knee arthroplasty.[3,4] Loosening of the prosthesis can also be the result of a low-grade infection.[7] The diagnosis of a periprosthetic joint infection in patients with signs of loosening around a TKA can be difficult.

In the present retrospective study we analyzed the characteristics of 149 patients with radiographic signs of loosening of a TKA that underwent a standardized diagnostic algorithm similar to the approach suggested by the American Academy of Hip and Knee surgeons.[10] According to the definition by the Musculoskeletal Infection Society all clinical and laboratory data was analyzed preoperatively.[13] According to this classification 32 patients (21.5%) were diagnosed with PJI and treated with a multiple stage revision surgery approach. 117 patients were diagnosed with AL and treated with a primary replantation effort. This approach for revisions of TKA is in line with the suggestions by other authors.[3,4]

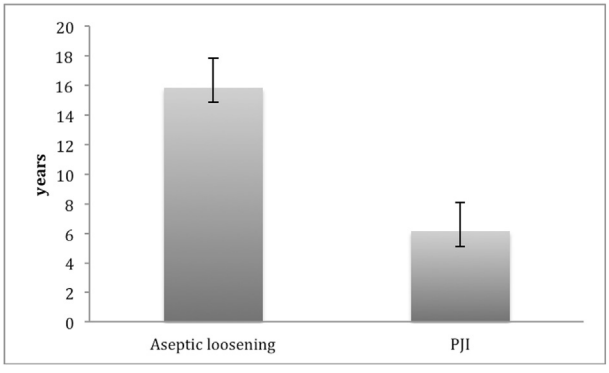

Fig. 2. ., Mean time between primary arthroplasty and joint aspiration.

Table 1
Demographic data.

	N	age	male	female	BMI
AL group	117	72.5 ± 8.8	37	80	25.9 ± 3.1
PJI group	32	73.9 ± 9.8	17	15	28.5 ± 3.3

There were no significant differences between both groups in age, gender distribution, and BMI ($p > 0.05$) (Table 1).

Table 2
Serologic testing, sv = standard value.

serology		AL group	PJI group
mean CRP (sv < 1 mg/dl)		0.45	7.85
	range	(0.32–1.95)	(1.99–15.4)
mean WBC/μl (sv = 4000-10000)		7514.27	8564.71
	range	(3200-12300)	(5506-14687)

Table 3
Mean aspirate results, PMN = synovial neutrophil percentage %.

	N	synovia cells/μl	PMN%
aseptic group range	117	1313 (100-2308)	38.9 (0-45)
PJI group range	32	28170 (3000-166006)	82.5 (65-94)

This study has some limitations, such as its retrospective character and a low sample size. Additional biomarkers such as α-defensin were not used in this study. Furthermore, we did not have information about possible revision surgery at other institutions.

The latency period between primary arthroplasty and presentation with symptomatic TKA loosening provides a diagnostic hint to differentiate between AL and PJI. In this study with an average latency period of 15.8 years patients with AL presented significantly later compared to patients with PJI (avg. 6 years). Other authors[14,15] presented similar finding in patients with aseptic loosening of TKA. Zu jedem Zitat einen Satz schreiben. The date of primary index TKA seems to be a very important hint towards the diagnosis and can help to reduce misdiagnosis of PJI.

In accordance with the definition by the Musculoskeletal Infection Society[16] patients were diagnosed with PJI when three of the following four measures were positive: blood CRP level of >1 mg/dl, synovial cell count >3000 cells/μl, synovial polymorphonuclear percentage >65%, and a bacterial growth from two synovial fluid aspirate cultures. Parvizi et al.[11] presented in 2018 the first validated evidence based criteria for diagnosing PJI after knee arthroplasty. However in our study the scoring system was not evaluated. D-dimer, and erythrocyte sedimentation rate, alpha-defensin, leukocyte esterase,and synovial CRP were not detected in our study. However, if it possible to detect all markers recommended by Parvizi et al.[11] in patients with radiographic signs of prosthetic loosening after TKA a PJI could be ruled out. Conversely in clinical practice it could be difficult to recieve all markers for the new diagnostic criteria by Parvizi et al. For example the α-defensin test, Synovasure (Zimmer Biomet), is rather expensive and not available worldwide, whereas measurement of synovial CRP is

Table 4
Sensitivity and specificity, CI = 95% confidence interval, + positive, - negative.

	cutoff	sensitivity	specificity
CC	>3000 cells/µl	0.84 (CI 0.81–0.87)	0.96 (CI 0.92–0.98)
PMN (%)	>65%	0.84 (CI 0.80–0.85)	0.94 (CI 0.90–0.97)
synovial fluid cultures	+/-	0.71 (CI 0.67–0.75)	1 (CI 0.98–1.1)
CRP	>1 mg/dl	0.84 (CI 0.81–0.86)	0.77 (CI 0.74–0.80)

comparably less expensive and broadly available.[17] Blood testing is a reasonable screening method in patients with symptomatic TKA. In all cases C-reactive protein (CRP) should be obtained.[18] At our institution erythrocyte sedimentation rate is not part of the standard testing and was not obtained in this study. In all patients with radiographic signs of loosening included in this study CRP and white blood cell count in the blood were obtained at initial presentation. The CRP values of patients with PJI were significantly higher compared to patients with AL. However, there was no significant difference in white blood cell count between the groups. The CRP test is cost-effective and highly sensitive with a reported sensitivity of 0.75–0.81.[19] In this study we were able to obtain a sensitivity of 0.84 (95% CI 0.81–0.86) with a good negative predictive value of 0.94. However, CRP values are limited because of their low specificity of 0.77. Due to its good negative predictive value in cases of symptomatic TKA loosening with negative CRP there is a low risk of PJI. In contrast positive CRP results are not specific but should presuppose an aspiration, analysis, and microbiological culture of the joint fluid. In this study all 149 patients with signs of loosening in TKA underwent a joint fluid aspiration independently of their serological CRP values. CRP may be negative even in cases of PJI. Therefore aspiration should always be performed in symptomatic TKA.[20] Another crucial measure is the synovial cell count (CC) that has been presented in multiple studies with excellent specificity and sensitivity for the diagnosis of PJI.[21–23] In this study the sensitivity of CC count for PJI in patients with radiographic signs of loosening was 0.84 (95% CI 0.81–0.87). These results are in line with the literature with sensitivity values reported between 0.78[24] and 0.94.[23] Also a high specificity of 0.96 (95% CI 0.92–0.98) could be shown in this study, that is also comparable to the existing literature.[22,24] Also the results obtained for the synovial fluid neutrophil percentage are comparable to the results reported in literature.[22–24] In summary, a high synovial cell count or a high synovial polymorphonuclear percentage confirm the diagnosis of PJI in patients with osteolysis around a TKA.

Microbiological cultures of the synovial fluid provide a high specificity but offer poor sensitivity for the diagnosis of PJI.[25,26] Whereas a positive culture confirms the diagnosis of an infection, a negative synovial fluid culture does not rule out the diagnosis PJI. Anaerobic and aerobic cultures of the synovial fluid aspirates were prepared in all 149 patients included. For the synovial fluid cultures in this study a low sensitivity of 0.71 (95% CI 0.67–0.75) with a high specificity of 1 (95% CI 0.98–1.1) was obtained for PJI. With specificity for synovial fluid cultures reported between 0.86[27] and 0.97[25] these results are comparable with the existing literature. Overall, synovial fluid cultures provide the single best mean to confirm the diagnosis of an infection, but offer poor sensitivity. Microbiological testing of five intraoperatively harvested periprosthetic soft tissue samples served as a retrospective control for the diagnosis of aseptic or septic loosening in our study. The approach used in this study was similar to the methodology presented by the American Academy of Hip and Knee surgeons in 2017. Using this method 117 patients were diagnosed with aseptic loosening. Of these patients three were positive in one of the five intraoperatively obtained soft tissue samples. We suspect that it is a consequence of contamination since these patients did not fulfil any other criteria for PJI. In all patients diagnosed with PJI based on the criteria including CC, PMN, and CRP a periprosthetic joint infection was confirmed by two or more positive intraoperative soft tissue samples retrospectively. Also, it has been suggested to base the diagnosis on cultures of soft tissue samples.

According to the current guidelines of the Musculoskeletal Infection Society[13] patients with radiographic signs of loosening were categorized in PJI and AL. However, other authors[21,23] suggest different threshold values, e.g. lower synovial cell counts in synovial fluid, to distinguish between these entities. This study, however, could show that these relatively simple measures provide the basis for a safe and reliable differential diagnosis between PJI and AL.

5. Conclusion

Using a meticulous diagnostic algorithm this study identified 21.5% of PJI in patients presenting with symptomatic loosening of TKA. Whereas the latency period between index TKA and loosening provides a diagnostic hint, the approach presented provides a safe and reliable tool to preoperatively detect a periprosthetic joint infection. We suggest that all patients with radiographic signs of loosening of a TKA receive blood testing for CRP, as well as an aspiration of joint fluid. The synovial fluid should be analyzed for synovial cell count, polymorphonuclear percentage, and synovial cultures.

Declarations of interest

None.

Founding

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Conflicts of interest

None.

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