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HIP ARTHROPLASTY

Incidence and risk factors for heterotopic ossification following periprosthetic joint infection of the hip

Thomas Rosteius[1] · Valentin Rausch[1] · Simon Pätzholz[2] · Sebastian Lotzien[1] · Hinnerk Baecker[1] · Thomas Armin Schildhauer[1] · Jan Geßmann[1]

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Abstract

Introduction Heterotopic ossifications (HOs) commonly occur following total hip arthroplasty. Data regarding the appearance of HO after periprosthetic joint infection (PJI) of the hip are rare. Therefore, the aim of this study was to analyze the incidence and potential risk factors for the development of HO in patients with PJI of the hip.

Materials and methods We performed a single-center, retrospective study including patients treated with a two- or multi-stage operation and patients undergoing salvage procedure in cases of PJI of the hip with a minimum follow-up of 6 months. A total of 150 patients were included in the analysis. The Brooker-scale was used to classify HO. Patients were divided in three groups: (1) No HO, (2) HO Brooker type 1–4, and (3) high-grade HO (HO Brooker type 3 and 4). In each group, we checked possible risk factors for the development of HO for statistical significance.

Results Patients included in our study had a mean age of 70.4 ± 12.1 years. Of all patients, 75 were women (50%). HOs could be found in 70 patients (46.7%). Twenty-seven patients showed HO Brooker type 1, 23 type 2, 15 type 3 and 5 type 4. Male gender [odds ratio (OR) 2.14; $p = 0.022$], smoking (OR 5.75; $p = 0.025$) were significant risk factors for HO. A chronic infection (OR 3.54; $p = 0.029$) and a higher number of procedures ($p = 0.009$) were significant risk factors for the development of high-grade HO.

Conclusions HOs often occur following surgical care of PJI. Male gender, smoking, a chronic infection and high number of operations are risk factors for developing HO after PJI.

Keywords Heterotopic ossification · Periprosthetic joint infection · Risk factors · Total hip arthroplasty · Revision hip arthroplasty

Introduction

Total hip arthroplasty (THA) is the most commonly performed joint replacement surgery in cases of osteoarthrosis of the hip [1]. Complications after THA are dislocation of the implant, intraoperative and periprosthetic fractures and wounds or joint infections of the hip [2, 3]. Another possible complication following THA is the occurrence of heterotopic ossifications (HOs). The incidence for HO after primary THA in the literature ranges from 5.2% up to 61.3% [4–8]. In case of revision THA even higher rates are described in the literature [9]. The extent of the HO can be classified using the Brooker scale [10]. This classification divides HO into 4 stages, based on the extent of the HO in the conventional X-ray images of the hip (Table 1). High-grade HO (Brooker 3 and 4) can lead to pain, limited range of motion and reduced function of the involved joint, possibly resulting in a complete ankylosis [7, 11]. Widely used prophylaxis strategies for HO include the intake of non-steroidal anti-inflammatory drugs (NSAIDs) that are also routinely used as part of the postoperative analgesia and postoperative radiation with proven significantly lower incidence and expression rates [12–15]. Compared with NSAIDs, radiation appears to be associated with lower

✉ Thomas Rosteius
thomas.rosteius@outlook.de

[1] Department of General and Trauma Surgery, BG University Hospital Bergmannsheil, Bürkle-de-la-Camp Platz 1, 44789 Bochum, Germany

[2] Department of Radiological Diagnostics, Interventional Radiology and Nuclear Medicine, BG University Hospital Bergmannsheil, Bürkle-de-la-Camp Platz 1, 44789 Bochum, Germany

Table 1 Brooker classification according to Brooker et al. [10]

Grade 1	Single ossifications around the hip
Grade 2	Bone projection of pelvis or proximal femur with more than 1 cm away from the opposite surface
Grade 3	Bone projection of pelvis or proximal femur with less than 1 cm away from the opposite surface
Grade 4	Hip ankylosis

risk rates for the most common side effects (fatal cancer vs. gastric bleeding or perforation) [16]. If HO has already occurred, the only therapeutic treatment option is surgical resection [17], which is especially challenging in revision surgery since the complication rate, especially for vascular and nerve injuries, is high [18] (Fig. 1).

HOs are described as abnormal benign lamellar bone formations in soft tissues combined with edema and swelling of the affected joint [6, 19]. The development of HO could be a consequence of an inappropriate differentiation of pluripotent mesenchymal stem cells. Several other proteins, such as BMP-4 or prostaglandin E2, also play roles in the development of HO [17]. However, the etiopathology of HO is still not fully understood. Several risk factors are discussed to play a central role in the development of HO, such as male gender, cemented implant, bilateral operations, ankylosing spondylitis, old age, history of HO on the contralateral site, lateral approach or pre-existing hip fusion [6, 8, 17]. In our clinical practice, the occurrence of HO is thought to be particularly high in revision arthroplasty following PJI. However, data regarding the frequency and specific risk factors in patients with PJI are not described in the literature. Therefore, our hypothesis for this study is that HO often occurs after PJI and that certain risk factors, including the infection itself, favor its development.

The aim of this study is to highlight incidence as a marker for the frequency of HO after PJI. In addition, possible risk factors that favor the formation of HO will be identified.

Materials and methods

We performed a single-center, retrospective study including all patients treated for PJI of the hip with a two- or multistage operation or undergoing salvage procedure with establishment of chronic fistula between 2008 and 2011 in our institution. Included were all patients with a PJI according the diagnostic algorithm of the American Academy of Orthopedic Surgeons [20]. Excluded were all patients with a follow-up of less than 6 months. Therefore, from 229 patients with diagnoses PJI of the hip, 79 patients were excluded because of missing follow-up, resulting in a total of 150 patients who met the criteria and were included in the analysis (Fig. 2). The Brooker scale [10, 21] (Table 1) was used to classify HOs. All images were graded independently by two experienced physicians in bone radiology (an orthopedic surgeon and a radiologist). The reviewers were blinded for the

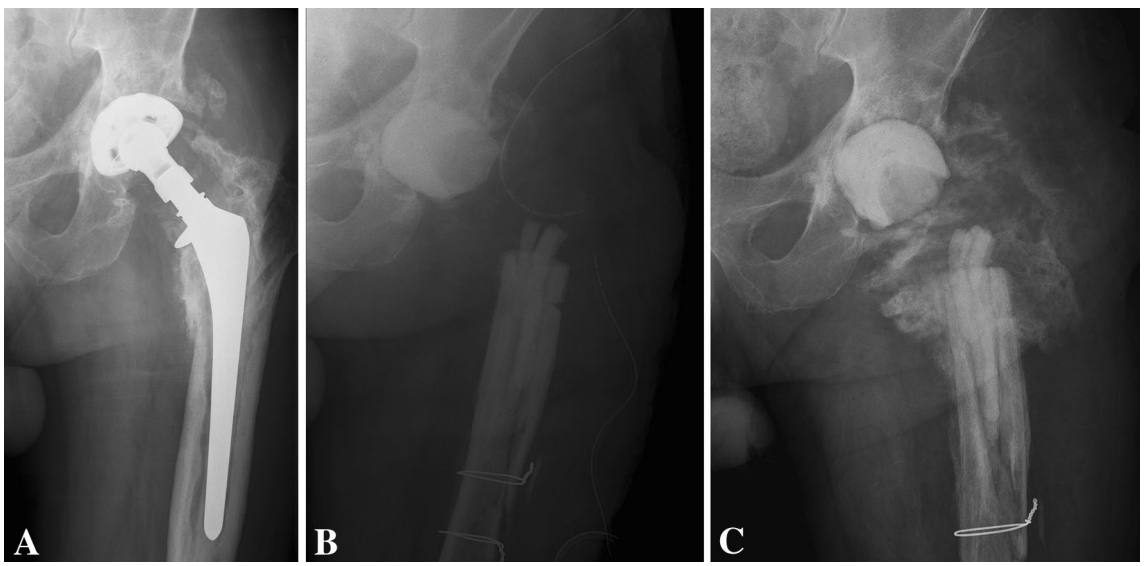

Fig. 1 Development of HO after explantation of THA in case of PJI. Figure 1 demonstrates an 81-year-old patient with the occurrence of PJI 5 years after implantation of the total hip arthroplasty (**a**). The postoperative radiograph after explantation of the prosthesis shows the implantation of a PMMA-cement spacer (**b**). Two months later, a high-grade HO (Brooker grade 3) developed with the cement spacer still in situ (**c**). Later on, only resection of the HO and explantation of the cement spacer with establishing of a definitive Girdlestone-situation was performed because the patient rejected further hip arthroplasty

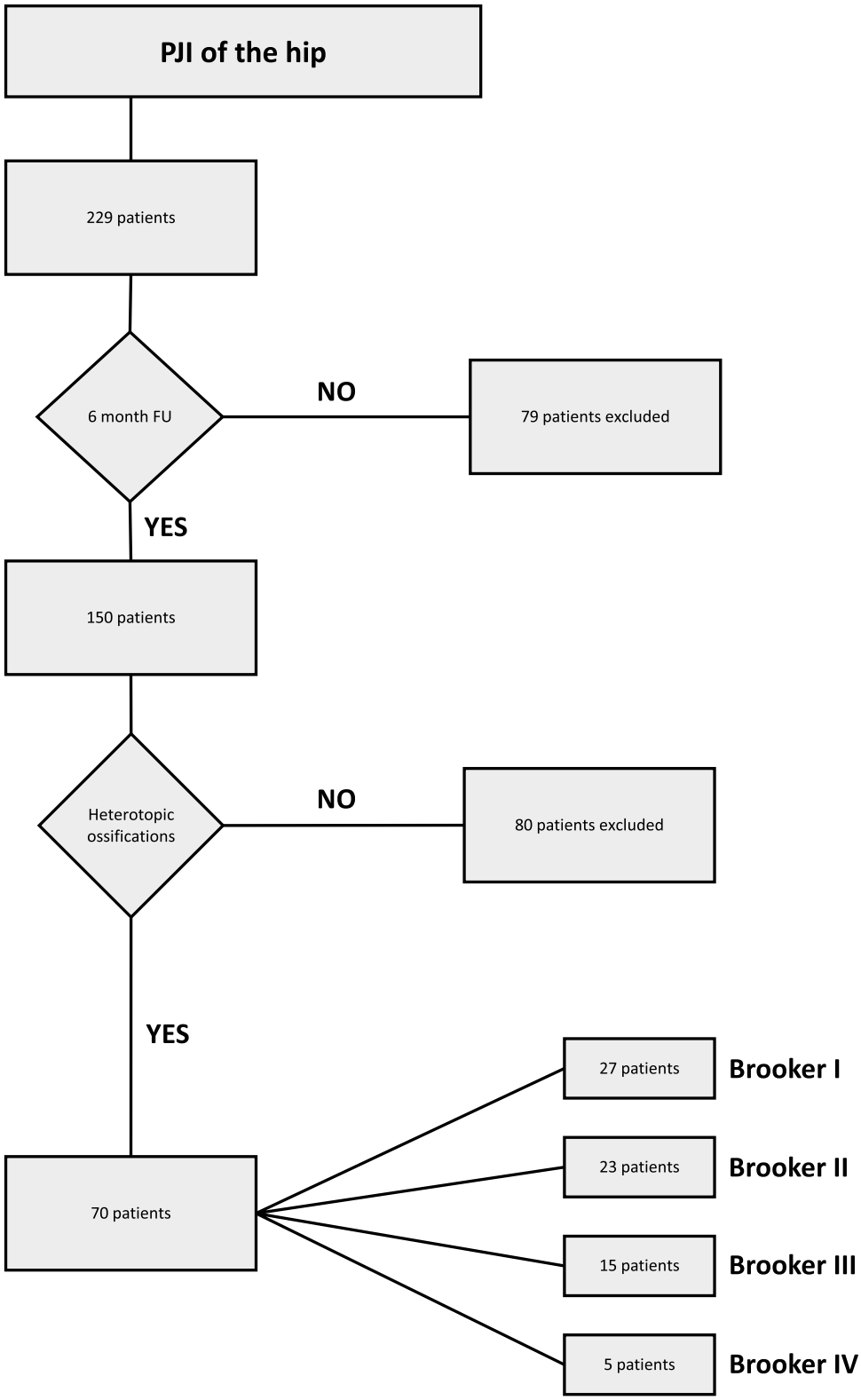

Fig. 2 Flowchart of the study protocol

grading of the other physician. In case of non-accordance, a consensus between both physicians was reached.

Perioperative medical management was similar in all patients including the routine use of NSAID's as part of the multimodal pain management. Postoperative thromboembolic prophylaxis was administered to all patients with certoparin or unfractionated heparin. To analyze possible risk factors in regards to the severity of HO, patients were

divided into three groups: (1) No HO (2) HO Brooker types 1–4 and (3) high- grade HO (HO Brooker types 3 and 4). According to the literature of the clinical significance of HO [7, 11], Brooker types 3 and 4 are believed to be the most relevant and were therefore subsumed as "high grade" HO. Differences in these groups regarding age, sex, body mass index (BMI), American Society of Anesthesiologists (ASA)-score, comorbidities, bacterial species, onset of the PJI, primary and revision THA, the procedure for treatment of PJI, the number of operations, the use of red packed blood cells and a persistent (chronic) infection at time of detection of the HO were statistically checked for significance. Persistent (chronic) infection was defined as either (a) the persistent detection of a microbial pathogen diagnosed by preoperative joint aspiration and/or intraoperative sampling following surgical explantation in case of PJI or (b) a continued existing fistula. Primary THA was defined as the first THA in the respective patient, whereas the second or further THA was defined as revision THA.

Statistical analysis

To analyze possible risk factors, we calculated the ORs (odds ratios) for HO and high-grade HO (Brooker 3–4) with a contingency table and the 95% confidence intervals (95% CIs). To demonstrate statistical significance, we used the Chi-square test or Fisher's exact test if appropriate. After testing for normal distribution of data using the Kolmogorov–Smirnov test, normally distributed variables were analyzed using the two-tailed *t* test. Non-normal variables were analyzed with the Mann–Whitney *U* test. Statistical significance was set to $\alpha = 0.05$.

Results

Of the included 150 patients, 75 were women and 75 were men. The mean age was 70.4 ± 12.1 years (range 33–91 years). The mean follow-up was 25.1 ± 27.7 months (range 6–120 months). Tables 2 and 3 show the clinical data separated for HO and high- grade HO. Of the 150 patients, in 79 (52.7%) patients, a primary prosthesis was infected, whereas 71 (47.3%) patients presented an infection of a revision prosthesis. All patients were treated surgically due to a PJI: in 119 cases (79.3%), a two- or multistage exchange operation with a PMMA spacer was performed. In 31 cases (20.7%), because of multimorbidity or specific patient request, only a debridement with establishing a chronic fistula as a salvage procedure in case of chronic PJI was performed. Of the 119 cases with a two- or multistage exchange operation, high-grade HO occurred in 18 cases (15.1%), whereas in the cases treated with a salvage procedure only 2 out of 31 patients developed high-grade HO (6.5%) ($p = 0.25$).

Table 2 Clinical data of patients with HO

	Clinical data				
	HO	No HO	OR	95% CI	*p* value
Age (years)	70.57 ± 11.5	70.22 ± 12.6			0.860
Sex			**2.14**	**1.11; 4.11**	**0.022***
Male	42	33			
Female	28	47			
ASA-score					0.518
I	2	5			
II	19	17			
III	36	36			
IV	3	6			
BMI (kg/m^2)	29.23 ± 5.0	27.51 ± 5.5			0.072
EK (*n*) (Median)	10.5 ± 14.7 7	7.4 ± 8.0 6			0.342
No. of operations (Median)	3.6 3	3.2 ± 3.3 2			0.158

BMI body mass index, *EK* packed red blood cells, *CI* confidence interval, *OR* odds ratio

*Statistical significance: $p < 0.05$

Of 150 patients, who were included in the analysis, 70 patients developed HO in the follow-up. Thus, the incidence of developing HO after PJI was 46.7%. The incidence of high-grade HO (Grade 3/4) was 13.3% (20/150).

Table 4 shows the difference in the expression of HO according to the Brooker scale of the total collective.

Tables 5 and 6 show the variables for HO and high-grade HO (Brooker 3/4), respectively, after PJI of the hip. Significant potential risk factors for developing HO were as follows: male sex [$p = 0.022$; OR 2.14 (95% CI 1.11; 4.11)] and smoking [$p = 0.025$; OR 5.75 (95% CI 1.20; 27.61)]. A significant potential risk factor for developing high-grade HO compared to low-grade HO or no HO was a persistent (chronic) infection [$p = 0.029$; OR 3.54 (95% CI 1.12; 11.15)]. There was also statistical significance regarding the number of operations in patients with high-grade HO (median 4 vs median 3, $p = 0.009$) (Table 3).

We found no statistically significant differences in the occurrence of HO based on the bacterial species.

Discussion

In our study, we examined the frequency of the occurrence of HO after operative treatment of PJI of the hip and investigated relevant risk factors in these patients. The incidence rates of HO and high-grade HO after PJI of the

Table 3 Clinical data of patients with high grade (Brooker 3/4) HO

	Clinical data 2				
	Brooker 3/4	No HO/Brooker1/2	OR	95% CI	*p* value
Age (years)	70.8 ± 13.3	70.3 ± 11.9			0.856
Sex			1.26	0.49; 3.25	0.631
Male	11	64			
Female	9	66			
ASA-score					0.469
I	2	5			
II	4	32			
III	8	64			
IV	2	7			
BMI (kg/m^2)	27.4 ± 3.2	28.5 ± 5.6			0.433
EK (*n*)	7.5 ± 20.5	6.0 ± 9.6			0.361
(Median)	4	3			
No. of operations	4.1 ± 1.8	3.3 ± 2.8			**0.009***
(Median)	**4**	**3**			

BMI body mass index, *EK* packed red blood cells, *CI* confidence interval, *OR* odds ratio

*Statistical significance: $p < 0.05$

Table 4 Differences in the expression of HO depending on the gender

	Brooker grade					
	No HO	1	2	3	4	Total
Female	47	11	8	9	0	75
Male	33	16	15	6	5	75
Total	80	27	23	15	5	150

Table 5 Variables for heterotopic ossification after PJI of the hip

	OR	95% CI	*p* value
Revision THA	1.22	0.64; 2.33	0.541
Late infection	0.67	0.23;1.98	0.469
DM with organ failure	6.08	0.69;53.33	0.098
DM without organ failure	1.78	0.80; 3.97	0.153
Polymicrobial infection	1.05	0.51; 2.16	0.902
Cerebrovasc. diseases	1.76	0.48;6.52	0.516
Smoking	**5.75**	**1.20; 27.61**	**0.025***
Renal insufficiency	1.92	0.70;5.28	0.198
Rheumatoid disease	0.75	0.20; 2.78	0.751
Chronic infection	1.44	0.75;2.76	0.271
Exchange surgery	1.08	0.49; 2.39	0.850

DM diabetes mellitus, *Cerebrovasc. diseases* TIA and Apoplex, *BMI* body mass index, *EK* packed red blood cells, *PMMA* polymethylmetacrylat, *OR* odds ratio, *CI* confidence interval

*Statistical significance: $p < 0.05$

Table 6 Variables for high grade (Brooker 3/4) heterotopic ossification after PJI of the hip

	OR	95% CI	*p* value
Revision THA	1.13	0.44; 2.90	0.798
Late infection	0.87	0.18; 4.20	1.000
DM with organ failure	1.32	0.15; 11.88	0.583
DM without organ failure	0.95	0.30; 3.10	1.000
Polymicrobial infection	1.58	0.58; 4.30	0.365
Cerebrovasc diseases	0.71	0.09; 5.91	1.000
Smoking	2.69	0.65; 11.14	0.166
Renal insufficiency	3.00	0.94; 9.60	0.068
Rheumatoid disease	0.71	0.09; 5.91	1.000
Chronic infection	**3.54**	**1.12; 11.15**	**0.029***
Exchange surgery	2.58	0.57; 11.80	0.252

DM diabetes mellitus, *Cerebrovasc diseases* TIA and Apoplex, *BMI* body mass index, *EK* packed red blood cells, *PMMA* polymethylmetacrylat, *OR* odds ratio, *CI* confidence interval

*Statistical significance: $p < 0.05$

hip were 46.7% and 13.3%, respectively. Statistically significant risk factors for the development of HO after PJI were male sex and smoking. A persistent infection and the number of operations were risk factors for high-grade HO (Brooker 3/4). The number of previous THA (primary or revision THA) or the exchange regime (two- or multistage vs. salvage-procedure) did not influence the development of HO (Tables 5, 6).

A large retrospective study by Higo et al. [4] and a meta-analysis by Zhu et al. [6] describe respective incidence rates of 5.2% and 30% after primary THA. This wide range could be due to the different methods of classification and heterogeneous patient populations [4]. Compared with the incidence of HO in these studies dealing with HO after primary THA [4, 6], the incidence rates in our group were markedly higher, at 46.7% for HO in general and 13.3% for high-grade HO. This is possibly due to a higher rate of known risk factors in our patients (e.g., male gender, high rate of intermittent PMMA-spacer) [7]. However, although inflammation is thought to be a risk factor for the development of HO, comparative data on the incidence of HO after PJI of the hip is rarely described in the literature. Therefore, the reasons for the high incidence of HO after PJI, even compared with the lower rates of HO after primary THA, still remain to be determined.

The etiology of the development of HO has not yet been completely understood. Three large groups are repeatedly described in the literature as having an increased risk of developing HO: patients with a spinal cord injury, patients with a cerebral injury and patients with extensive tissue trauma, such as after joint surgery. It is believed that the tissue trauma induces a local inflammation, leading to several signaling pathways with the participation of different proteins [22, 23]. Therefore, the high rate of HO in PJI could be due to several factors: The basic principle of the treatment of a PJI is radical debridement. Thus, radical debridement of a soft tissue trauma could be the cause of the high incidence of HO after PJI [2, 23]. This is also supported by our results, demonstrating a higher number of surgical procedures in patients with high-grade HO. Secondly, since local inflammation seems to play a central role, an infection as the cause of an inflammatory immune reaction might also play a role in the development of HO in joint infections. This is somewhat supported by the significantly higher rates of high-grade HO in chronic infection and the generally high incidence of HO in our study. However, the incidence of high-grade HO is also prominently higher in relation to the number of operations. Therefore, more operations that result in a higher tissue trauma are a major confounding factor. As such, a differentiation between the chronic infection and the operational trauma as reason for higher HO-rates is nearly impossible.

To our knowledge, Manrique et al. [24] published the only clinical study on this topic so far [24]. They also demonstrated that patients undergoing surgical care of hip PJI seem to be at increased risk of developing HO compared to aseptic failure [24]. The incidence of overall HO in PJI and aseptic groups in their study was 84% (47/56 patients) and 11% (12/112 patients), respectively. High-grade HO (grades 3 and 4) in PJI and aseptic groups were 25% (24/56 patients) and 4% (4/112 patients), respectively [24].

Beyond this, there are basic science studies in the literature that suspect infection as a trigger in the development of HO. For example, bacterial colonization has been considered a potential early risk factor for combat injury-induced HO formation [25, 26]. Mo et al. [27] studied the effect of bacterial toxins on the osteogenic differentiation of mesenchymal stem cells (MSCs). They exposed MSCs with osteogenesis induction medium and lipopolysaccharide (LPS) from *Escherichia coli* (toxin). Their results demonstrate a paradoxical upregulation of osteogenic activities, which might result in the development of HO in some patients [27]. Seybold et al. [28] demonstrated that osteogenic differentiation of expanded MSCs in vitro can be promoted by bacterial LPS-stimulated leukocytes [28].

The bacterial species contaminating a wound could also seem to influence the occurrence of HO. In an animal study, Pavey et al. [23] investigated the link between bioburden (bacterial contamination) and HO. In a blast-related HO model, a significantly greater volume of HO was observed in rats infected with MRSA when compared with *A.baumanii* or vehicle (without containing bacteria) after 12 weeks. The authors concluded that bioburden with MRSA results in a greater volume of ectopic bone formation, which may be the result of chronic soft tissue inflammation. Therefore, early wound bacterial colonization may be a key risk factor for increased ossification [23]. In our study, the pathogenic species (e.g., MRSA), in contrast to the duration of the infection (chronic infection), did not influence the occurrence of HO.

To analyze possible risk factors, we have divided the collective into three groups according to the general occurrence of HO and, because of more clinical relevance [7], to the grade of HO following the Brooker classification.

We could show that smoking is associated with higher rates of the development of HOs. This is thought to be associated with increased neurohumoral activation and generalized increased inflammation (e.g., like diabetes) [29, 30] which would again support the theory of increased inflammation as a key factor in the development of HO. Additionally, our demonstration of significantly higher rates of high-grade HO's in case of chronic infections supports the often described phenomenon of infection-triggered HO formation.

Not least in clinical practice, surgeons treating patients with PJI should be aware of the high incidence of HO in these patients since HO formation, such as in the exchange interval, can lead to problems and increased complication rates in further operations [18], e.g., vascular and nerve lesions and extended surgery time due to HO resection. Thus, as a consequence of this study, patients with PJI should thoroughly evaluated for the necessity of HO-prophylaxis regimes. This could include a prophylactic radiation after two- or multistage exchange surgery in selected cases with increased risk of HO due to existing accompanying factors.

This study has several limitations. First, the study was designed as a retrospective study. However, the authors believe that this limitation outweigh the large patient collective rendering valid results. Moreover, in the authors' experience, PJI are often only diagnosed and operated in an emergency setting making a prospective inclusion nearly impossible. The high rate of patients with lack of follow up (79 patients) is to be considered a confounder. In our collective, several risk factors described in the literature are combined, such as male gender or the use of cement [6, 31], which was used in all patients with two-or multistage procedures in our study. This could lead to a bias towards a higher rate of HOs in these patients [7]. Furthermore, since not only persistence of the infection but also the number of operations influence the development of high-grade HO, we could not determine the effect of each individual factor. Therefore, individual influence cannot be attributed. Patients who did not screen positive for HO did not receive further screening for HO using radiography at a defined follow-up. Those patients may theoretically develop HO later on. However, HO is believed to reach its complete formation after 6–12 weeks post-operatively [17, 32] with the radiographic evolution of HO completed during a 6-month interval in most cases [33]. In our study, the minimum follow-up was, therefore, set to 6 months. Finally, the relatively small size of the high-grade HO cohort may have resulted in a type II error that failed to reveal the statistical significance of some variables.

Conclusion

Patients with surgical care of PJI are at considerable high risk for the development of HO. Beyond already known risk factors, specific patient populations seem to be at particular risk for developing HO after PJI, with it being understood that in these cases, a multifactorial genesis is probable. HO prophylaxis may be recommendable in eligible patients undergoing surgical intervention for PJI of the hip. Clinical evidence for an association between bacterial species and formation of HO could not be proven, but might be answered in multicenter prospective studies.

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Compliance with ethical standards

Conflict of interest All authors confirm that there is no conflict of interest.

Ethical statement There is a positive statement of the Institutional Review Board for this work (Registered number 4669-13).

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