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ORIGINAL ARTICLE

18F FDG-PET/CT has poor diagnostic accuracy in diagnosing shoulder PJI

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Abstract

Purpose Chronic low-grade periprosthetic joint infection (PJI) of a shoulder replacement can be challenging to diagnose. 18F-FDG PET/CT is suggested as a modality to diagnose lower-limb PJI, but no studies on shoulder replacements exist. The aim of this study was therefore to determine the diagnostic accuracy of 18F-FDG PET/CT in diagnosing chronic PJI of the shoulder.

Methods Patients evaluated for a failed shoulder replacement during a 3-year period were prospectively included in the study. All patients underwent pre-operative 18F-FDG PET/CT, and were evaluated for signs of infection by three independent reviewers using shoulder-specific criteria. Interrater-agreement was calculated between the reviewers. If the patient had revision surgery, biopsy specimens were obtained and cultured with bacterial growth in the cultures serving as gold standard of infection.

Results A total of 86 patients were included in the study. Nine patients were 18F-FDG PET/CT positive for infection, with only three true positive. Using the gold standard, infection was diagnosed after revision surgery in 22 cases. All infections were chronic and caused by low-virulent microbes. The sensitivity of 18F-FDG PET/CT was 0.14 95% CI (0.03–0.36), specificity 0.91 95% CI (0.81–0.97), positive predictive value was 0.40 95% CI (0.15–0.71) and negative predictive value 0.71 95% CI (0.67–0.75). The inter-observer agreement was 0.56 (Fleiss' kappa), indicating moderate agreement of the visual FDG-PET evaluation using the shoulder-specific criteria.

Conclusion 18F-FDG PET/CT has poor diagnostic accuracy in diagnosing low-grade PJI of the shoulder. 18F-FDG PET/CT cannot be recommended as a part of the routine preoperative workup to diagnose low-grade infection of a shoulder replacement.

Keywords FDG-PET · PJI · Infection · Shoulder · Periprosthetic joint infection

Introduction

The incidence of shoulder joint replacement surgery is expected to increase considerably due to increased life-expectancy and physical demands of senior citizens. Consequently, the absolute number of patients with complications, such as periprosthetic joint infection (PJI), is likely to increase. PJI of the shoulder is a rare, but critical condition. It can lead to prolonged morbidity, additional operations, and a reduction in functional outcome [1, 2].

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PJI incidence is reported to range from 1% to up to 5% after primary total shoulder joint replacement [1, 3]. However, studies investigating routine cultures from aseptic revisions or removal of presumably non-infected hardware from the shoulder girdle report a positive culture-rate of up to 29% [4–6]. This high rate of unexpected positive cultures raises a concern of underdiagnosed low-grade shoulder PJI, since multiple positive cultures are regarded as a strong indicator of infection [7, 8].

PJIs are a challenge to diagnose clinically, because chronic low-grade infection often mimics symptoms of aseptic loosening [9]. Traditionally, the preoperative diagnostic workup consists of blood tests, synovial markers, aspiration, and conventional imaging, but these tests are neither specific nor sensitive for chronic PJI [10, 11]. So far, no single test or composite variables have been able to diagnose low-grade PJI preoperatively with high sensitivity, including radionuclide imaging, which is occasionally used to diagnose PJI. A recently published consensus paper investigated the use of advanced imaging in diagnosing PJI, and concluded that level 1 and 2 evidence is sparse, making solid recommendations difficult to give [12]. Currently, white blood cell/bone marrow (WBC/BM) SPECT CT imaging is considered the optimal radionuclide imaging technique in lower limb arthroplasties [13, 14]. However, it is debatable whether this is a favorable modality for shoulder PJIs, as evidenced by the poor results of our own recently published study [15] . In addition, WBC/BM SPEC CT is a complex and time-consuming procedure with a considerable radiation burden. Consequently, simpler functional imaging techniques are highly warranted.

An attractive alternative is ^{18}F-FDG PET/CT (FDG-PET), which has proven effective in diagnosing orthopedic and vascular graft infections [16]. First, the spatial resolution of FDG-PET outperforms gamma camera scintigraphy, theoretically improving the possibility of detecting the exact anatomical location of any infectious foci in cases with several implant components, such as total shoulder replacements [17]. Second, FDG-PET has several practical advantages, including far simpler patient and scanner logistics. Third, FDG-PET can be performed with the use of considerably less ionizing radiation than WBC/BM scintigraphy. Fourth, the diagnostic accuracy of FDG-PET to diagnose hip PJI has been shown in some studies to be high [18]. However, to our knowledge, no studies have examined the diagnostic performance of FDG-PET on failed shoulder replacements.

The aim of this study was therefore to assess the diagnostic performance of ^{18}F-FDG PET/CT in diagnosing chronic low-grade infection of failed shoulder replacements by measures of sensitivity, specificity, positive predictive value (PPV), and negative predicted value (NPV).

Material and methods

Study design

The study was a prospective, nationwide, cohort study conducted on consecutive patients with a failed shoulder replacement during the period 1st October 2015 to 30th September 2017.

In Denmark, all 5.7 million citizens have free and universal access to health care. Two public orthopedic departments are by law appointed as the only departments allowed to revise shoulder joint replacements. Patients with a failed shoulder arthroplasty are (mandatorily) referred to these two departments by general practitioners or other orthopedic departments.

The study was approved by the Local Ethical Scientific Committee (ref. no. 1–10–72-229-15) and the Danish Data Protection Agency (ref. no 1–16–02-567-13).

Study population

During the study period, all patients ($n = 292$) referred to the two departments with a failed shoulder replacement were informed about the study. Patients were included if a written consent was obtained, excluding patients with failure due to acute fracture, traumatic dislocation of the arthroplasty, or prior ipsilateral revision surgery due to chronic PJI. After enrolment, patients completed a standardized preoperative workup consisting of joint aspiration, radiographic assessment,

PJI positive if at least one primary sign exists OR at least two secondary signs exist.

Primary signs

1)There is a sinus tract communicating with the prosthesis

2)A pathogen is isolated by culture from at least three separate tissue or fluid samples obtained from the affected prosthetic joint

OR

Secondary signs

a) Elevated serum C-reactive protein (CRP) OR erythrocyte sedimentation rate OR White blood cell count
b) A single positive culture
c) Positive PET/CT imaging
d) Unexplained nightly pain OR excessive joint stiffness

Fig. 1 Modified MSIS PJI definition (mMSIS)

serum inflammatory markers (erythrocyte sedimentation rate, white blood cell count, and C-reactive protein) and FDG-PET. After completion of the FDG-PET scan, an outpatient visit was conducted, in which all diagnostic tests were reviewed and a tentative diagnosis of infection was set based on the modified Musculoskeletal Infection Society definition (MSIS) shown in Fig. 1. Revision surgery was recommended based on three conditions: i) if FDG-PET strongly indicated infection, ii) if the biochemistry or physical assessment indicated infection, or iii) if signs of component loosening was found, or obvious mechanical dysfunction was observed on conventional imaging. Patients willing to accept limitations of shoulder joint movement and level of pain, as well as patients in whom surgical treatment was not recommended, were omitted from the study ($n = 57$). A flow-chart of patient inclusion is presented in Fig. 2.

The remaining 86 patients underwent revision and comprised the diagnostic accuracy study cohort. Thus, all patients had a pre-operative FDG PET, and cultures of tissue-specimens obtained during the revision served as clinical diagnosis of infection. Baseline patient demographics are presented in Table 1.

Definition of true infection status

In order to assess the diagnostic accuracy of FDG-PET, a diagnostic gold standard in PJI is required. However, no such standard exists [19]. This study defined PJI as growth of the same organism in cultures from at least three of five separate biopsy specimens obtained during revision. The specimens were obtained with clean utensils from areas showing signs of infection, according to the method described by Kamme-Linberg et al. [20]. If no signs of infection were obvious, specimens were obtained from five random isolated intraarticular spots. All biopsy specimens were cultured for 4 days for aerobic bacteria and a further 10 days for anaerobic bacteria, the latter to detect slow-growing bacteria such as Cutibacterium acnes (C. acnes, formerly known as Proprionibacterium acnes). Any therapy with antibiotics was halted 2 weeks prior to revision surgery, and perioperative antibiotics were withheld until all biopsies were obtained. Both steps were implemented to reduce the risk of false negative results owing to iatrogenic suppression of bacterial growth.

Image acquisitions

PET/CT scans were performed on a Siemens Biograph 64 PET/CT (Erlangen, Germany). All patients fasted at least 6 h before the procedure. Bedside PET fasting blood glucose > 11 mmol/l was not accepted. In both centers, imaging was performed 60 min after intravenous administration of the radiotracer. An initial low-dose CT without contrast enhancement (50 mAs) was performed, in order to correct for photon attenuation and to co-localize FDG uptake and anatomical structures. At Center One, the FDG PET was performed from

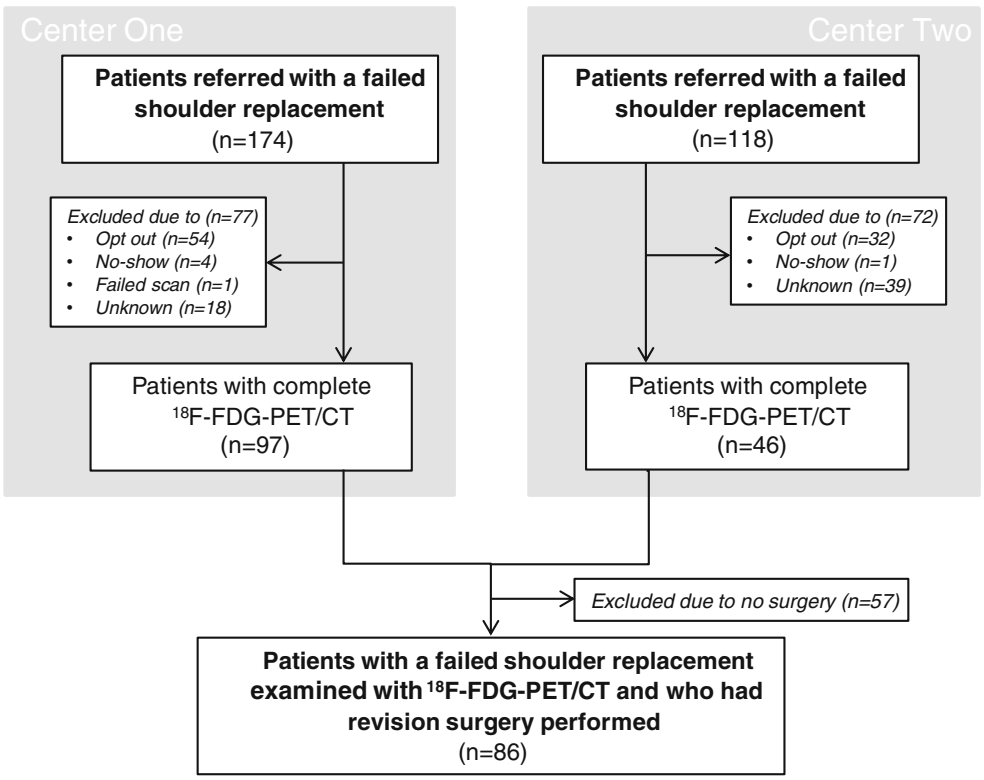

Fig. 2 Patient inclusion

Table 1 Demographics

		Referred	No consent	Excluded	Study group
No. of patients		292	149	57	86
Mean age (range)		68 (34–89)	69 (45–87)	68 (34–89)	67 (42–85)
Gender: *n* (%)	Female	182 (62%)	91 (61%)	28 (49%) *	63 (73%)
	Male	110 (38%)	58 (39%)	29 (51%) *	23 (27%)
Prosthesis age (mean)		4.2 years	4.6 years	3.8 years	4.5 years
Revision rate: % (*n*)		47% (137)	30% (45)	0% (0)	100% (86)
Infection rate % (*n*)		27% (38)	33% (16)	NA	26% (22)

*$p < 0.05$. Statistical difference compared to study group

elbow to basis cranii (4 MBq ^{18}F-FDG kg^{-1}; 2 min per bed position in three-dimensional mode) and at Center Two, from the mid-thigh to the skull (5 MBq 18F-FDG kg^{-1}; 3 min per bed position in three-dimensional mode). Both centers adhered to international guidelines [21].

Reconstruction of attenuation-corrected images was done using visually comparable, ordered subset expectation maximisation algorithms with point-spread function (PSF) (Siemens Biograph: Four iterations, 21 subsets, 3-mm Gaussian post-processing filter, matrix size 336 × 336). The estimated dose of radiation per patient was 9.5 mSv at Center One and 12.8 mSv at Center Two.

Image analysis

All images were reviewed using first attenuation-corrected images and in equivocal cases subsequently non-attenuation corrected images.

First, a senior ortho-nuclear consultant blinded for results of the preoperative work-up made an initial assessment of FDG-PET scans. Based on the consultants' experience from other cases of orthopedic or implant infections, an initial dichotomized diagnosis (infection/no infection) was set based on pattern of activity. This initial diagnosis, referred to as "best practice", was used due to the lack of a standardized algorithm for evaluating PJI in shoulders with FDG-PET.

Second, we developed a set of criteria to diagnose infection by the FDG-PET, hereafter referred to as "shoulder-specific assessment". This shoulder-specific assessment was constructed using the knowledge of initial observed patterns of activity compared with the true infection status, rate-of-loosening of the stem and cavitas components in shoulder replacements, and the criteria published by Reinartz in 2005 proposed for FDG-PET evaluation of PJI in hip arthroplasties [22]. The shoulder-specific assessment dictates that FDG-PET was positive for infection if at least one of the following patterns of activity were observed: i) increased FDG uptake in soft tissue adjoining the joint cavity, ii) increased FDG uptake along the humoral stem, or iii) increased uptake in regional lymph nodes near the affected shoulder. Examples of such patterns of activity are shown in Fig. 3.

Third, all scans were reassessed using the shoulder-specific assessment by three consultants blinded for the previous FDG-PET results. Subsequently, a new dichotomous FDG-PET diagnosis was made based on majority decision, e.g., if one reviewer judged the scan negative and two reviewers positive, the new status was positive.

Statistical analysis

Sensitivity, specificity, PPV, and NPV of FDG-PET were calculated using the microbial diagnosis as true infectious status (reference standard). All results are reported as fractions with 95% confidence intervals (CI).

Interobserver agreement was evaluated using kappa statistics for multiple raters per patient, a method put forward by Fleiss in 1971 [23]. A kappa value of zero indicates agreement as expected by chance. Kappa values were graded as poor (0.00–0.20), fair (0.21–0.40), moderate (0.41–60), good (0.61–0.80) and excellent > 0.81 [24].

Data was analyzed using STATA 15, StataCorp, College Station, TX, USA.

Results

Cultures of biopsy specimens from revisions found that 22 patients were infected. Table 2 shows pre- and perioperative observation for these patients. The most frequent isolated bacterium was Cutibacterium acnes in 17 cases, followed by *Staphylococcus epidermidis* in two cases, and one case of infection caused by each of the following; Staphylococcus hominis, Staphylococcus capitis, and unclassified coagulase-negative staphylococcus. We have enclosed a full overview of the culture results in all the infected cases and examples of different classification criteria for infection in Supplementary file 1.

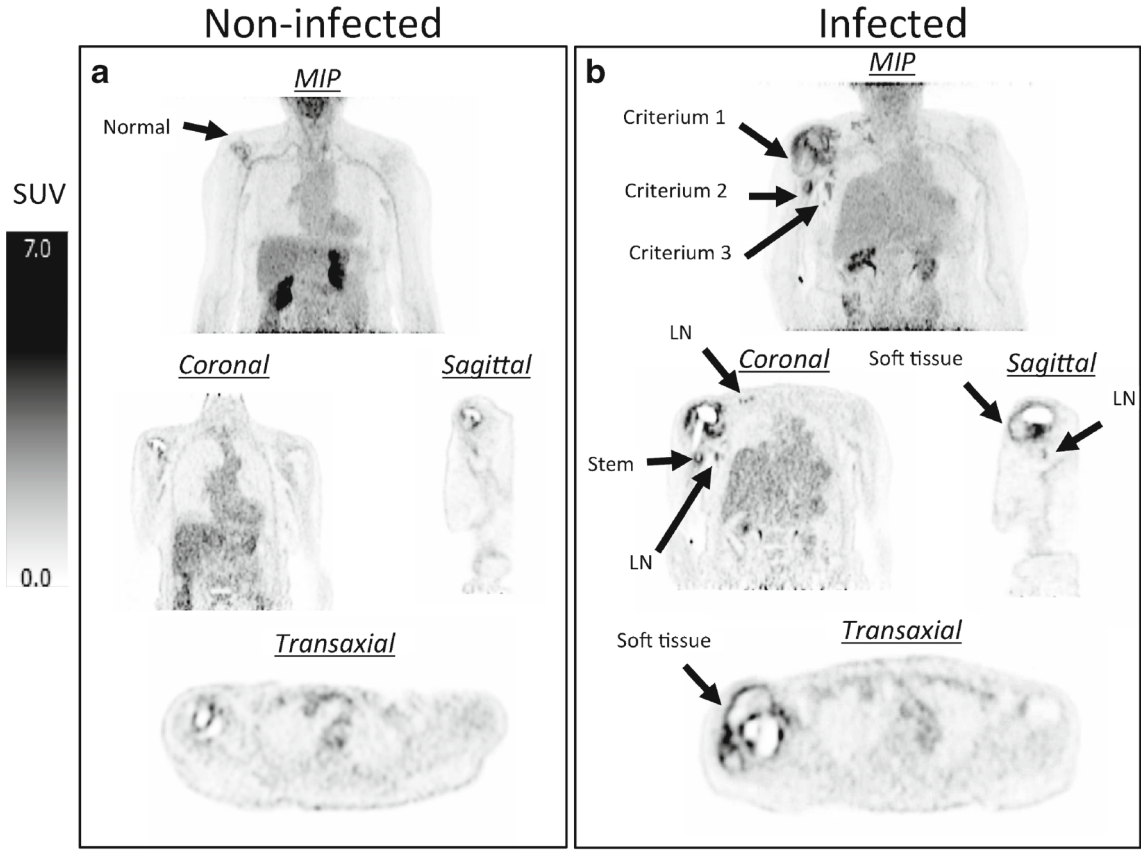

Fig. 3 Examples of criteria 1 to 3 of shoulder-specific FDG-PET assessment; *SUV* Standard Uptake Value, *LN* Lymph node, *MIP* Maximal Intensity Projection; Criterion 1 increased FDG uptake in soft tissue adjoining the joint cavity; Criterion 2 increased FDG uptake along the humoral stem; Criterion 3 increased uptake in regional lymph nodes near the affected shoulder

The mean time from last arthroplasty-related surgery to FDG-PET imaging was 4.6 years for the infected group and 4.4 years for the non-infected group ($p > 0.05$).

Using the shoulder-specific assessment, nine patients were diagnosed as infected. Three scans were true positive, six false positive, 19 false negative, and 58 true negative. Representative examples of scans are shown in Fig. 4. This results in a sensitivity of 0.14 (95% CI: 0.03–0.36) and specificity of 0.91 (95% CI: 0.81–0.97). The PPV and NPV was 0.40 (95% CI: 0.15–0.71) and 0.71 (95% CI: 0.67–0-75). Results are summarized in Tables 3, 4, and 5. The results stratified by center can be found in Table 7 (online supplementary file 2).

The overall agreement of infection diagnosis based on the shoulder-specific assessment among the three reviewers was 0.56 (Fleiss' kappa) indicating moderate inter-observer agreement. The shoulder-specific assessment contained three patterns of activity which each defined infection. When investigating the sub-criteria in the shoulder-specific assessment, the inter-observer agreement of pathologic tracer uptake in soft tissue adjoining the shoulder joint was 0.34 (fair); agreement of pathologic uptake along the stem was 0.61 (good), and for regional lymph nodes 0.57(moderate).

Discussion

The main finding of our study is that FDG-PET performs poorly in diagnosing chronic low-grade PJI of the shoulder, even with introduction of joint-specific patterns of FDG uptake previously demonstrated to perform well in lower limb prosthetic infections. In addition, the overall agreement between the three reviewers of the FDG-PET scans using the shoulder-specific assessment was only moderate, and agreement on soft-tissue tracer uptake near the joint (criterion 1) was even worse. This is hardly surprising, since prosthesis-near FDG activity varies significantly even in non-infected and well-fixed implants [25]. However, we also observed only mediocre agreement of such distinct patterns of activity as uptake along the humoral stem (criterion 2) and uptake in regional lymph nodes (criterion 3), further underscoring the difficulty in assessing the images. Such poor results suggest that any alterations in peri-prosthetic FDG uptake caused by low-grade infections are discrete, and that visual discrimination between pathological and normal FDG uptake is virtually impossible.

Table 2 Details on serum markers and perioperative observations in all infected patients

Patient number	C-reactive protein (mg/l, < 8)	White blood cell count (10^9/l, < 10.0)	Sedimentation rate (mm/h, < 30)	Majority FDG-PET diagnose	Perioperative suspicion of infection
1	1.3	6.2	11	No infection	None
2	12.6	5.17	12	No infection	None
3	22	5	22	No infection	None
4	4.5	6.84	27	No infection	None
5	2.7	9.42	1	No infection	None
6	0.5	5.59	7	No infection	None
7	4	10	16	No infection	None
8	19	9.7	34	Infection	Infection[a]
9	0.5	11.8	4	No infection	None
10	0.5	9.5	2	No infection	None
11	0.5	7.1	6	No infection	None
12	0.5	3.6	7	Infection	Infection[b]
13	0.5	7.8	16	No infection	None
14	0.5	6.4	6	No infection	None
15	0.5.	9.7	23	No infection	None
16	N/A	N/A	N/A	No infection	None
17	0.5	7.5	8	No infection	None
18	0.5	5.4	13	No infection	None
19	0.5	5.7	11	No infection	None
20	44	6.7	56	Infection	Infection[c]
21	0.5	11.2	5	No infection	None
22	0	N/A	2	No infection	None

[a] membranes and cloudy fluid, [b] membranes and pus, [c] membranes, cloudy fluid, and pus

Mixed results have been reported on FDG-PET's performance in detecting PJI of the lower limb, and the usefulness of FDG-PET in this setting is still debatable [26]. Verberne et al. reported in a review from 2016 that FDG-PET could predict PJI of hip replacements with a sensitivity and specificity of 83% and 91% [27]. FDG-PET also appears to perform poorer in knee compared to hip replacements. Verberne et al. reported in a meta-analysis from 2017 a specificity of 84% and a sensitivity of 70% and Mayer-Wagner et al. a sensitivity of 14% and specificity of 89% [28, 29]. However, the latter was based on a very small amount of material. Our diagnostic performance is markedly inferior to any study on failed hip replacements, which may partly be attributed to the definition of infection and to different microbiology. Whereas our reference standard was positive cultures in at least three of five specimens, other studies have defined infection as one positive biopsy or a combination of histopathology and microbiology [27, 30, 31]. Our more rigorous definition of infection was chosen to reduce the risk of misclassifying perioperative contamination as infection [8]. Despite the obvious lack of consensus, we have chosen to treat patients as infected if three or more separate biopsy specimens turn positive for the same bacteria, until clear guidelines on how to interpret cultures with low virulent microbes is presented.

Another factor with considerable impact on the diagnostic FDG-PET performance is the criteria applied to evaluate the pattern of pathological activity [32]. A set of criteria for failed hip replacements were developed by Reinartz et al. in 2005 [22]. It defines infection as increased FDG uptake in the periprosthetic tissue, whereas increased uptake along the stem is considered indicative of loosening. However, differentiation between aseptic and septic loosening was not possible. The inability to differentiate the cause of loosening is probably related to the polyethylene debris from wear of the prosthesis components. The inflammatory cells seen in areas with polyethylene wear or bone remodeling will cause increased FDG uptake, just as activated leucocytes in areas of infection would [28]. Since load bearing, risk of aseptic stem-loosening, and microbiology are different in hips compared to shoulders, application of these criteria without modification to our settings is questionable. In the shoulder, aseptic loosening of the humeral component is rare, and as a consequence the risk of false-positive scans from aseptic stem-loosening seem limited [33]. On the glenoid side, component loosening is more frequent, and signs of loosening, e.g., radiolucent lines on conventional imaging are not uncommon [34]. In our cohort, ten

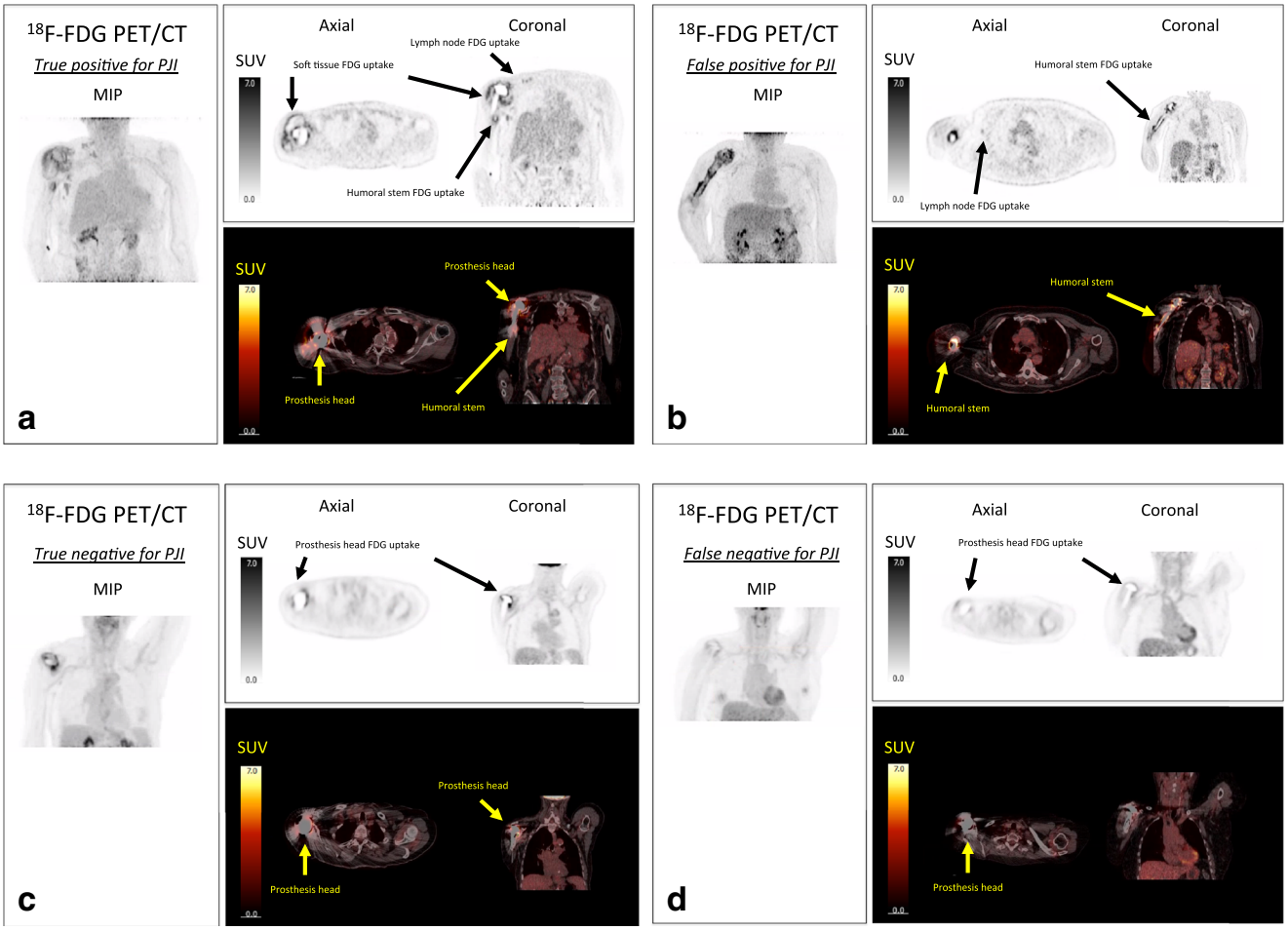

Fig. 4 Shoulder-specific assessment on representative examples of FDG-PET images; All images are attenuation corrected; a True positive scan. +Lymph node activity, + Humoral stem activity, + Soft tissue activity, positive cultures; b False positive scan. +Lymph node activity, + Humoral stem activity, - Soft tissue activity, no growth; c True negative scan. - Lymph node activity, - Humoral stem activity, - Soft tissue activity, no growth in cultures; d False negative scan. -Lymph node activity, - Humoral stem activity, - Soft tissue activity, positive

glenoid components were found to be loose; two of these shoulders were infected, but none showed increased activity on the PET scan. Thus, omitting evaluation of activity near the glenoid component in our shoulder-specific assessment does not decrease the probability of diagnosing infection.

Table 3 FDG-PET diagnosis using shoulder-specific-assessment[a] vs. true infection

	FDG-PET diagnosis		
Infection diagnosis based on biopsies	Negative	Positive	
No infection	58	6	64
Infection	19	3	22
	77	9	86

[a] Majority diagnose

Table 4 Diagnostic performance of FDG-PET using shoulder-specific assessment[a]

Sensitivity	0.14 95%CI: 0.03–0.35
Specificity	0.91 95%CI: 0.81–0.97
PPV	0.38 95%CI: 0.15–0.70
NPV	0.71 95%CI: 0.67–0.75

[a] Majority diagnose

Table 5 Serum markers and mMSIS status compared to FDG-PET and true infection diagnosis

	Infection		No injection	
	True positive[a] ($n = 3$)	False negative[a] ($n = 19$)	True negative[a] ($n = 58$)	False positive[a] ($n = 6$)
Serum markers[b]				
C-reactive protein (mg/l)[c]	19 (< 0.6–44)	< 0.6 (< 0.6–22)	1.2 (< 0.6–16.9)	9 (4.8–59)
Sedimentation rate (mm/h)	34 (7–56)	8 (1–27)	10 (2–67)	38.5 (5–54)
White blood cell count (10^9/l)	6.7 (3.6–9.7)	8.9 (4.7–12.9)	6.9 (3.7–10.7)	7.3 (5–11.8)
Infection status measured by modified MSIS criterion				
mMSIS status with postoperative information	3 positives	18 positives	53 negatives 5 positives	1 negative 5 positives
mMSIS with only preoperative information	2 positives 1 negative	18 negatives	57 negatives 1 positive	1 negative 5 positives

[a] FDG-PET diagnose measured by majority diagnose of Shoulder-Specific assessment, [b] median (range), [c] lowest detection level 0.6 mg/l

This study has several strengths. The most important is the short time-frame and prospective nature of inclusion, which ensured unaltered diagnostic modalities in the form of PET/CT scanner systems, reconstruction protocols, and microbiology cultures. Furthermore, despite shoulder revisions being less common that hip and knee revisions, the nationwide approach resulted in a high number of included patients. Last, the FDG-PET scans were performed on all patients as a screening procedure. This reduced the risk of selection bias in the study group, since no selection of patients occurred before inclusion.

A limitation of this study is the presence of culture-negative infections. This entity is thought to make up approximately 20% of revised joint replacements, and encompass cases in which no microbes can be identified despite strong clinical suspicion of infection [35]. Two of our six false-positive cases were culture-negative infections, since both patients were revised with a two-staged approach due to strong clinical suspicion of infection; but no growth was demonstrated. These culture-negative infections further illustrate the difficulties of choosing a gold standard of PJI to reference the diagnostic test. Sample images of the six false-positive cases and relevant clinical information can be found in Supplementary file 3.

The findings of this study suggest that FDG-PET has a limited place in the preoperative infectious work-up of shoulder PJI. However, due to the high prevalence of C. acnes infection of shoulders these results should be extrapolated with caution to cases with other orthopedic implants. Low virulent PJI have shown to produce less leucocyte migration to the infected joint, compared to more aggressive infections with, for example, *Staphylococcus aureus* [36–38]. Since the majority of infections in our cohort were caused by low virulent microbes, these two factors together could offer a possible explanation for the difficulty of detecting enhanced tracer uptake in infected patients. Despite this, we were able to identify two C. acnes and one *Staphylococcus epidermidis* infections.

Conclusion

Failure of a shoulder arthroplasty due to chronic low-grade infection poses a significant diagnostic challenge with an array of modalities used in the preoperative workup. In this study, we have presented data showing that FDG-PET has poor diagnostic accuracy in diagnosing chronic infection of shoulder joint replacement. Despite use of shoulder-specific criteria for evaluating the FDG-PET scans, the diagnostic performance was low. Our results lead us to conclude that FDG-PET should not constitute a routine part, if any, in the preoperative investigations of failed shoulder arthroplasties.

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Authors' contributions TFJ conceived the study, collected data, analyzed data, and drafted the manuscript. JL participated in conceiving the study, and revised the manuscript. HD revised the manuscript. MHV reviewed images. BZ reviewed images and revised the manuscript. JOV collected data and revised the manuscript. KS participated in conceiving the study, and revised the final manuscript. AKS collected data and revised the manuscript. LCG participated in conceiving the study, reviewed images, and revised the manuscript. All authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest Author T Falstie-Jensen declares that he has no conflict of interest. Author J Lange declares that he has no conflict of interest. Author H Daugaard declares that he has no conflict of interest. Author MH Vendelbo declares that he has no conflict of interest. AKB Sørensen declares that she has no conflict of interest. Author B Zerahn declares that he has no conflict of interest. Author J Ovesen declares that she has no conflict of interest. Author K Søballe declares that he has no conflict of interest. Author LC Gormsen declares that he has no conflict of interest.

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Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee (ref. no. 1–10–72-229-15) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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