PET/CT to detect adverse reactions to metal debris in patients with metal-on-metal hip arthroplasty: an exploratory prospective study

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Summary
Metal-on-metal (MoM) bearings in total hip arthroplasties and hip resurfacing arthroplasties have recently shown a new type of complication: adverse reactions to metal debris (ARMD). ARMD is characterized by local severe inflammation and tissue necrosis leading to implant failures. The gluteal muscle region is important for the patient outcome after revision surgery. This prospective positron emission tomography/computed tomography (PET/CT) study was undertaken to evaluate the characteristics of 2-deoxy-2-[18F]fluoro-D-glucose ([18F]FDG) and [68Ga]Gallium citrate ([68Ga]Citrate) PET/CT in ARMD patients. [18F]FDG and [68Ga]Citrate PET/CT were performed in 18 hip arthroplasty patients: 12 ARMD patients (with 16 MoM hips) and six arthroplasty controls without ARMD. Tracer uptake was evaluated visually, and maximum standardized uptake (SUVmax) was measured in the gluteal muscle region. ARMD severity was graded by metal artefact reduction sequence-magnetic resonance imaging (MARS-MRI). Periprosthetic [18F]FDG uptake was observed in 15 of 16 hips, [68Ga]Citrate uptake in three of 16 hips, respectively. The distribution of tracer uptake resembled infection in three hips. In the gluteal muscle region, the SUVmax of [18F]FDG was significantly greater in hips with moderate and severe ARMD compared with the controls (P = 0.009 for [18F]FDG and P = 0.217 for [68Ga]Citrate). In patients who needed revision surgery, an intraoperative finding of gluteal muscle necrosis was associated with increased local SUVmax as detected by preoperative [18F]FDG (P = 0.039), but not by [68Ga]Citrate (P = 0.301). In conclusion, the inflammatory reaction to metal debris in hip arthroplasty patients is best visualized with [18F]FDG.

Introduction
Hip arthroplasty is one of the most successful surgical procedures and is associated with a low prevalence of complications (Learmonth et al., 2007). One of the most critical issues is the selection of articulating bearing surfaces (Rajpura et al., 2014). Metal-on-metal (MoM) bearings have been designed to improve endurance (Bozic et al., 2012). Over 1 million patients worldwide have received MoM bearings, either in the form of hip resurfacing arthroplasty or total hip arthroplasty (THA). Reported complications associated with hip prostheses using MoM bearings have been unexpected (Rising et al., 2012). Compared with alternative types of bearings, hip prostheses with MoM bearings have shown a 2–3-times higher prevalence of failure and ≤30% prevalence of reoperation at 10 years (Murray et al., 2012; Smith et al., 2012). This is well above the current standard; the prevalence of failure should be ≤5% at 10 years. Certain MoM hip prostheses have been withdrawn from the market, whereas those with the best-registered record of survival remain in use.

Early failures of hip prostheses with MoM bearings are due to an entirely new complication: adverse reactions to metal debris (ARMD). This term is used for varying degrees of local tissue reactions in and around the joint: acute and chronic inflammation, necrosis and fibrin deposition (Langton et al., 2011; Mittal et al., 2013). The pathophysiology of ARMD is multifactorial and may be due (at least in part) to a hypersensitivity reaction (Pandit et al., 2008). There are no definitive diagnostic criteria for ARMD.

Metal artefact reduction sequence-magnetic resonance imaging (MARS-MRI) can be used to detect the characteristic diagnostic findings of ARMD, including accumulation of

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periprosthetic fluid; cystic and solid areas of tissue necrosis and pseudotumours; oedema and atrophy of muscle; avulsion of gluteal tendons (Anderson et al., 2011; Hauptfleisch et al., 2012). Muscle disease in the gluteal region is probably secondary to the inflammation associated with ARMD; irreversible; associated with poor outcome in revision surgery (Daniel et al., 2012; Berber et al., 2015). Therefore, patients with large pseudotumours and/or high blood levels of metal ions should be considered for revision surgery or should remain under annual surveillance (Matharu et al., 2016).

The clinical presentation and diagnosis of ARMD can be challenging (Lombardi et al., 2012). Even large pseudotumours of ARMD can be asymptomatic (Williams et al., 2011). The metal particles and ions released from MoM hip joints can affect the immune response to infection (Hosman et al., 2010). Clinically, ARMD may mimic an indolent periprosthetic joint infection (PJI); these two conditions may even coexist (Blumenfeld et al., 2010). Tests to distinguish between ARMD and a PJI are lacking (Della Valle et al., 2010; Wyles et al., 2013).

2-Deoxy-2-[18F]fluoro-D-glucose ([18F]FDG) is the most commonly used tracer for combined positron emission tomography and computed tomography (PET/CT). It is generally used for cancer imaging, but [18F]FDG is also useful in imaging of infection as it is taken up by macrophages in areas of inflammation (Kubota et al., 1992; Zhuang & Alavi, 2002). In 2011, an imaging case report of [18F]FDG PET/CT in a patient with ARMD showed rim-like [18F]FDG uptake in the inflammatory pseudo-capsule, whereas the necrotic interior was almost entirely photopenic (Makis et al., 2011).

Gallium behaves as an in vivo iron mimetic that is picked up by sites showing acute/chronic inflammation and tumours (Kumar et al., 2012). While traditional [68Ga]Citrate, a gamma emitter with a half-life of 78 h, required scintigraphic imaging over as long as 72 h, [68Ga]Citrate is a positron emitter with a half-life of just 68 min, allowing rapid sectional imaging using PET/CT (Nanni et al., 2010; Roivainen et al., 2012). [68Ga]Citrate has shown promising results in the detection of skeletal infections and tumours (Mäkinen et al., 2005; Nanni et al., 2010; Behr et al., 2016).

Diagnostic and management algorithms contain no guidance for the use of nuclear imaging modalities in ARMD (Lombardi et al., 2012; Hannemann et al., 2013).

This study was designed as a head-to-head comparison of [18F]FDG and [68Ga]Citrate PET/CT in hip arthroplasty patients suffering from ARMD.

**Methods**

The present study is registered in the ClinicalTrials.gov database (NCT01970228). The study protocol was approved by the local institutional review board and Ethical Committee of the Hospital District of Southwest Finland, Turku, Finland (decision #81/180/2012). All participants provided written informed consent.

### Patients

ARMD patients were recruited from a population of hip arthroplasty patients (n = 2203) who were recalled for safety evaluation of MoM bearings at Turku University Hospital (Turku, Finland). Patients who had symptoms and/or functional impairment were selected to undergo MARS-MRI according to national guidelines. If the MARS-MRI was in keeping with ARMD, the patient was asked to participate in the PET/CT study.

The inclusion criterion was adult hip arthroplasty patients with American Society of Anesthesiology score I–III. The exclusion criteria were any related condition of the index hip which necessitated immediate surgical intervention, such as a septic infection or a periprosthetic fracture.

The selected subjects represented a consecutive sample of eligible patients. This was an exploratory prospective study for which a power analysis was not carried out.

The planned recruitment of ARMD patients (n = 10 and 2 additional patients to replace any withdrawal from the study) was undertaken between October 2012 and May 2013.

Based on the criteria of Reinartz et al. (2005), six symptomatic hip arthroplasty patients without ARMD were recruited as controls (four females and two males with a mean age of 66.8 ± 3.2 years) (Fig. 1). There were five controls with unilateral THA and one control with bilateral THA. Five controls had conventional bearings and one had MoM bearings. The time elapsed from their THA to PET/CT was 3.4 ± 2.4 years.

### Hip implants of adverse reactions to metal debris patients

All of 12 ARMD patients had MoM bearings in either THA or hip resurfacing arthroplasty. Five patients had unilateral THA and two patients had bilateral THA with cemenless femoral stem and acetabular cup components with MoM bearings. The nine hips comprised seven large-diameter M2a-Birmingham hip resurfacing and another two patients had bilateral hip resurfacing arthroplasties, all of which were Birmingham hip resurfacing implants (Smith and Nephew, Memphis, TN, USA) and two Durom Cup implants (Zimmer, Warsaw, IN, USA). Another three patients had unilateral hip resurfacing arthroplasties, and another two patients had bilateral hip resurfacing arthroplasties, all of which were Birmingham hip resurfacing implants (Smith and Nephew, Memphis, TN, USA). The mean time from primary surgery to PET/CT was 6.8 (range, 1.7–10.1) years.

### Clinical assessment and screening blood tests

All patients underwent clinical examination and routine imaging of their hips. Local symptoms such as pain were assessed using a questionnaire and visual analogue scale (VAS) of pain. The Western Ontario and McMaster Universities Osteoarthritis Index score (WOMAC) was used to evaluate functional disability on a scale from 0 (asymptomatic) to 100 (extremely...
symptomatic). Patients were excluded for having a PJI by following the current guidelines of the American Academy of Orthopaedic Surgeons (Della Valle et al., 2010), including the measurement of the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) and, if indicated, fluid aspiration of the hip joint under fluoroscopy. Serum levels of cobalt and chromium were determined, and the threshold values for unilateral and bilateral hip resurfacing arthroplasties were applied (Van der Straeten et al., 2013).

Metal artefact reduction sequence-magnetic resonance imaging

All patients had a normal glomerular filtration rate. The patients underwent MARS-MRI with contrast medium using 1.5-T scanners and recommended imaging protocols (Hart et al., 2009; Yanny et al., 2012). The severity of ARMD-related changes in periprosthetic soft tissue on MARS-MRI was classified using the grading system described by Anderson et al. (2011) (Table 1).

Acquisition of positron emission tomography and computed tomography images

After a 6-h fast, patients were studied by PET/CT. Patients were encouraged to drink water before study commencement. PET/CT (Discovery VCT; General Electric Medical Systems, Milwaukee, WI, USA) was carried out on the same day starting with $[^{68}\text{Ga}]$Citrate PET/CT and followed, 6-h later, with $[^{18}\text{F}]$FDG PET/CT. The Discovery VCT system had a 64-slice CT portion and a PET portion based on crystals of bismuth germanium oxide. The injected radioactivity dose of $[^{68}\text{Ga}]$Citrate was 186 ± 10 MBq, and image acquisition of the hips (10 min per bed position for 1–2 bed positions) began 60 min after injection. The intravenous dose of $[^{18}\text{F}]$FDG was 243 ± 14 MBq. Patients were scanned for 5 min per bed position, and 1–2 bed positions were required to cover the entire hip prosthesis. Imaging began 45 min after injection. Low-dose CT was used for attenuation correction (at settings of 120 kV, ≤80 mAs, and noise index of 25). The radiation-effective dose of the $[^{68}\text{Ga}]$Citrate injection was estimated to
Octreotide (i.e., 4/C1[18F]FDG injection was 4/C1[18F]FDG in the periprosthetic soft tissue, indicating a PJI. The sign of mechanical loosening of the prosthesis; 5 the acetabular cup and/or in the wide parts of the stem as in the femoral neck and whole prosthesis.

[68Ga]Citrate PET/CT images were analysed with an OsiriX PRO workstation (Aycan Medical Systems, Rochester, NY, USA). Non-attenuation-corrected PET images were also analysed.

Analyses of positron emission tomography and computed tomography images

Transaxial, coronal and sagittal images for visual analyses of the data were corrected for dead time, decay and photon attenuation. PET images were reconstructed using a fully three-dimensional maximum-likelihood ordered subset expectation maximization algorithm with two iterations, 28 subsets and a 6-0-mm full-width half-maximum postfilter. The matrix size was 128 × 128 in a 70-cm transaxial field of view, which yielded a pixel size of 5-5 × 5-5 mm. [18F]FDG and [68Ga]Citrate PET/CT images were analysed with an OsiriX PRO workstation (Aycan Medical Systems, Rochester, NY, USA). Non-attenuation-corrected PET images were also analysed.

Qualitative visual analyses of tracer distribution in periprosthetic regions were classified according to the system of (Reinartz et al., 2005), which was developed to evaluate PET images in patients with painful THAs. The descriptive patterns used in this classification were as follows: 1 – no increase in [18F]FDG uptake at the prosthesis–bone interface; 2 – increased uptake of [18F]FDG in the area around the femoral neck; 3 – increased uptake of [18F]FDG in the femoral neck and parts of the prosthesis–bone interface of the acetabular cup and/or proximal stem; 4 – increased uptake of [18F]FDG in the femoral neck and whole prosthesis–bone interface of the acetabular cup and/or in the wide parts of the stem as a sign of mechanical loosening of the prosthesis; 5 – uptake of [18F]FDG in the periprosthetic soft tissue, indicating a PJI. The measurement of the maximum standardized uptake value (SUVmax) was focussed on the region of interest (ROI) in the gluteal muscles with the highest uptake, and the SUVmax was calculated.

Table 1 Classification for metal-on-metal (MoM) disease on magnetic resonance imaging performed with metal artefact reduction sequences (MARS-MRI) (Anderson et al., 2011).

| Grade | Description | Criteria |
|-------|-------------|----------|
| A | Normal or acceptable | Normal postoperative appearances including seromas and small haematomas |
| B | Infection | Fluid filled cavity with high signal T2 wall; inflammatory changes in soft tissues, +/− bone marrow oedema |
| C1 | Mild MoM disease | Periprosthetic soft-tissue mass with no hyperintense T2W fluid signal or fluid filled periprosthetic cavity; either less than 5 cm maximum diameter |
| C2 | Moderate MoM disease | Periprosthetic soft-tissue mass/fluid filled cavity greater than 5 cm diameter or C1 lesion with either of following: (i) muscle atrophy or oedema in any muscle other than short external rotators or (ii) bone marrow oedema: hyperintense on short tau inversion recovery sequences (STIR) |
| C3 | Severe MoM disease | Any of the following: (i) fluid filled cavity extending through deep fascia, (ii) a tendon avulsion, (iii) intermediate T1W soft-tissue cortical or marrow signal, (iv) fracture |

Analyses of positron emission tomography and computed tomography images

The treating orthopaedic surgeons were blinded to the SUVmax values of the tracers. During the follow-up (≥3 years after imaging and ≥5 years after implantation), seven patients underwent revision surgery. The time elapsed from PET/CT to revision surgery varied between 1 and 46 months (median 4 months). Four of seven (57%) revision surgical procedures had an intraoperative finding (microscopic or macroscopic) of necrosis in the gluteal muscles (Table 2). Intraoperative tissue samples were submitted for microbiological and histopathological analyses. All samples were negative for bacterial infection. Removed implant components were also negative for the enhanced exclusion of biofilm-type infection using ultrasonic vibration (Gomez & Patel, 2011).

Statistical analyses

Statistical analyses were undertaken using Prism v7.01 (GraphPad, La Jolla, CA, USA). The SUVmax data, expressed as the mean ± standard deviation (SD), were tested for normality using the Shapiro–Wilk test. For analyses of data with a normal distribution, the independent-sample t-test was applied to test the significance of differences between two groups. The nonparametric Kruskal–Wallis test was applied for the comparison of two subgroups (no/mild and moderate/severe) of ARMD patients with the controls. A P value<0-05 (two-sided) was considered significant.

Results

All 12 recruited patients with ARMD (Table 2) completed the study. The most frequently reported symptoms were ‘pain upon exercise’ (11/12, 92%), ‘morning stiffness’ (11/12, 92%), ‘night pain’ (8/12, 67%), ‘night sweats’ (7/12, 58%), ‘sensation of heat’ (6/12, 50%), ‘chills’ (4/12, 33%), ‘fever’
The ARMD patients (n = 12) had unilateral MoM hips and four had bilateral MoM hips. Thus, the 12 patients had 16 MoM hips. MARS-MRI images (Table 3) revealed that all 12 patients suffered from ARMD in at least one hip. Of the 16 MoM hips, 14 were affected by ARMD. In four patients with bilateral MoM hips, two of these cases had ARMD bilaterally and two had ARMD unilaterally. Twelve (75%) hips showed moderate (grade C2) or severe (grade C3) ARMD. No hips had MARS-MRI findings that suggested infection (grade B). Eight MoM hips had thin-walled fluid collections, and six MoM hips had thick-walled and cystic areas of inflammation that formed pseudotumours.

Table 3 Metal artefact reduction sequence-magnetic resonance imaging (MARS-MRI) results and positron emission tomography combined with computed tomography (PET/CT) tracer distribution (n = 16).

### Characteristic

| Characteristic | Value |
|----------------|-------|
| Age (years)    | 64.6 ± 5.5 |
| Gender         |       |
| Male           | 7 (58%) |
| Female         | 5 (42%) |
| Laterality of hip arthroplasty |        |
| Right hip      | 5 (42%) |
| Left hip       | 3 (25%) |
| Bilateral      | 4 (33%) |
| Type of hip arthroplasty with MoM bearings |        |
| Total hip arthroplasty | 9 (56%) |
| Unilateral     | 5     |
| Bilateral      | 4     |
| Hip resurfacing arthroplasty | 7 (44%) |
| Unilateral     | 3     |
| Bilateral      | 4     |
| Time elapsed from operation to PET/CT (years) | 6.8 ± 2.0 |
| VASb (0–10)    | 4.7 ± 2.5 |
| WOMACc score (0–100) | 32 ± 14 |
| CRP and/or ESR values |       |
| Above cut-off valuesd | 3 (25%) |
| Below cut-off valuesd | 9 (75%) |
| Serum levels of cobalt and chromium |        |
| Above the recommended threshold valuesd | 10 (83%) |
| Below the recommended threshold valuesd | 2 (17%) |
| Revision surgery in follow-up |       |
| Yes            | 7 (44%) |
| Intraoperative gluteal necrosis | 4 (25%) |
| No intraoperative gluteal necrosis | 3 (19%) |
| No             | 9 (56%) |

Values are means ± SD or n (%).

bVisual analogue scale of pain from 0 (no pain) to 10 (worst imaginable pain).

A classification according to Anderson et al. (2011).

bClassification according to Reinartz et al. (2005).

(4/12, 33%) and ‘mechanical sensations’ (3/12, 25%). Three patients had increased CRP levels (range, 16–21 mg l⁻¹) and/or increased ESR values (range, 32–46 mm h⁻¹). As recommended (Della Valle et al., 2010), these patients underwent fluid aspiration of the hip joint to rule out infection. All cultures of joint fluid were negative. Ten patients had serum levels of cobalt and chromium that exceeded threshold values (Van der Straeten et al., 2013).

Eight ARMD patients had a unilateral MoM hip and four had bilateral MoM hips. Thus, the 12 patients had 16 MoM hips. MARS-MRI images (Table 3) revealed that all 12 patients suffered from ARMD in at least one hip. Of the 16 MoM hips, 14 were affected by ARMD. In four patients with bilateral MoM hips, two of these cases had ARMD bilaterally and two had ARMD unilaterally. Twelve (75%) hips showed moderate (grade C2) or severe (grade C3) ARMD. No hips had MARS-MRI findings that suggested infection (grade B). Eight MoM hips had thin-walled fluid collections, and six MoM hips had thick-walled and cystic areas of inflammation that formed pseudotumours.

**[18F]FDG positron emission tomography and computed tomography**

Table 3 shows the pattern of [18F]FDG uptake observed in the MoM hips of patients with ARMD. Only one hip did not show any [18F]FDG uptake in the periprosthetic area. The most common finding in 12 (75%) of 16 hips was tracer uptake in the area of the femoral neck alone (pattern 2) or tracer uptake in the femoral neck and parts of the prosthesis–bone interface (pattern 3). The distribution of [18F]FDG uptake in the periprosthetic soft tissues (especially in the gluteal muscles) resembled a pattern seen typically in infection of three (19%) hips (Fig. 2a). These accumulations were also verified on non-attenuation-corrected images, and only one patient was regarded as showing false-positive tracer uptake due to CT-based attenuation correction artefact in soft tissues.

In the gluteal muscle region, the SUV_max values of [18F] FDG were significantly greater in hips with moderate or severe ARMD compared with hips of the controls (P = 0.009) (Fig. 3). Patients who had necrosis in the gluteal muscles...
upon revision surgery showed significantly ($P = 0.039$) greater $SUV_{\text{max}}$ values of $[^{18}\text{F}]\text{FDG}$ compared with patients who had no necrosis in the gluteal muscles (Fig. 4). There was no statistically significance ($P = 0.164$) in $SUV_{\text{max}}$ of $[^{18}\text{F}]\text{FDG}$ between patients who needed revision surgery within the follow-up period ($n = 7$) and patients who did not ($n = 5$) ($3.43 \pm 1.75$ and $2.38 \pm 1.11$, respectively).

$[^{68}\text{Ga}]\text{Citrate}$ positron emission tomography and computed tomography

The visually interpreted uptake of $[^{68}\text{Ga}]\text{Citrate}$ remained negative (pattern 1) in 13 (81%) of 16 hips (Table 3). Three hips with increased uptake of $[^{68}\text{Ga}]\text{Citrate}$ (pattern 3 or 5) were found in the same three patients who showed a pattern of $[^{18}\text{F}]\text{FDG}$ uptake that suggested infection (pattern 5).

In the gluteal muscle region, the $SUV_{\text{max}}$ values of $[^{68}\text{Ga}]\text{Citrate}$ were not significantly different in hips with moderate or severe ARMD than in the control hips ($P = 0.116$). The $SUV_{\text{max}}$ values of $[^{68}\text{Ga}]\text{Citrate}$ were not significantly different in patients with an intraoperative finding of gluteal muscle necrosis compared with patients with no necrosis of the gluteal muscles ($P = 0.301$) or who did not need revision surgery (Fig. 4).

$[^{18}\text{F}]\text{FDG}$ and $[^{68}\text{Ga}]\text{Citrate}$ positron emission tomography and computed tomography of control hip arthroplasty patients

The confirmed diagnoses of the controls are shown in Fig. 1. Two controls had increased CRP and/or ESR values above the cut-off values. Four controls underwent fluid aspiration of the hip joint due to the suspicion of a PJI. Eventually, only one patient had positive culture of the synovial fluid. $[^{68}\text{Ga}]\text{Citrate}$ PET/CT correctly (pattern 3 according to the Reinartz et al. classification) identified this single case of a low-grade PJI caused by Staphylococcus epidermidis, which was associated with normal levels of CRP and ESR. The only control patient with MoM bearings had recurrent skin reactions in the region of the surgical scar and underwent extensive studies (bone scintigraphy, leucocyte scan, MARS-MRI, repeated fluid aspirations of the hip joint and skin biopsies) which ruled out periprosthetic infection, mechanical loosening and ARMD.

Five controls without infection or mechanical loosening showed a normal pattern of tracer uptake in the periprosthetic region (pattern 1 according to the Reinartz et al. classification) upon $[^{18}\text{F}]\text{FDG}$ and $[^{68}\text{Ga}]\text{Citrate}$ PET/CT (Fig. 2b). Two of these cases had slight uptake of $[^{18}\text{F}]\text{FDG}$ over the trochanter major as a sign of local bursitis.

The controls, including the patient with low-grade PJI, showed low uptake in the gluteal region. The $SUV_{\text{max}}$ values of $[^{18}\text{F}]\text{FDG}$ and $[^{68}\text{Ga}]\text{Citrate}$ were $1.18 \pm 0.21$ and $1.25 \pm 0.35$, respectively (Fig. 3).

Discussion

The present study was designed to characterize $[^{18}\text{F}]\text{FDG}$ and $[^{68}\text{Ga}]\text{Citrate}$ PET/CT findings in hip arthroplasty patients who suffered ARMD due to MoM bearings. We found
significantly increased uptake of $^{[18F]}$FDG in the gluteal muscle region in patients with moderate or severe ARMD. The pattern of tracer distribution mimicked infection in three hips. Such cases suggest that the scans may not be able to exclude a PJI in ARMD with severe inflammation and necrosis.

The selection of the gluteal muscle region for the measurement of SUV$_{max}$ was based on clinical relevance. The hip abductors are critical for the normal function and stability of the joint after hip arthroplasty. The gluteal muscles and tendons are affected frequently by the metal-wear debris of ARMD and cause functional deficits (Hosman et al., 2010) and a high prevalence of complications upon revision surgery (Grammatopolous et al., 2009). Therefore, screening of ARMD patients should accurately detect changes in the gluteal muscles and help to identify patients who need immediate surgical intervention (Berber et al., 2015): $^{[18F]}$FDG PET/CT may fulfil this requirement.

The increased uptake of $^{[18F]}$FDG in hips with moderate or severe ARMD was likely related to the extent of aseptic, necrotizing inflammation. Thus, $^{[18F]}$FDG might be useful for monitoring ARMD activity, along with the information provided by MARS-MRI. Treatment decisions (i.e., to carry out or not carry out revision surgery) are difficult in ARMD cases (Matharu et al., 2016). Patients are also hesitant to have
revision surgery if they are asymptomatic. Further studies are required to clarify if measurement of the local uptake of \(^{18}\text{F}\)FDG in the gluteal region could be used to identify patients who are in need of timely revision surgery before irreversible damage to the gluteal muscles occurs.

Only one hip with ARMD did not show any \(^{18}\text{F}\)FDG accumulation. Likewise, there was no uptake of \(^{68}\text{Ga}\)Citrate. This patient presented with only mild symptoms and serum levels of cobalt and chromium that were not increased. However, MARS-MRI showed moderate ARMD with a collection of periprosthetic fluid of maximum diameter of 7 cm. Muscle atrophy was not evident. During a follow-up of 9.5 years after the hip arthroplasty, the symptoms have not worsened and the patient has not been scheduled for revision surgery. In this patient, the lack of tracer uptake could be interpreted as a sign of stable ARMD without major inflammation in the periprosthetic area.

As a tracer that could be employed for diagnosing infection sites, \(^{68}\text{Ga}\)Citrate gave no extra value to the imaging of ARMD patients compared with \(^{18}\text{F}\)FDG. Further studies with \(^{68}\text{Ga}\)Citrate in ARMD patients do not seem to be warranted. However, the present study does not exclude the potential value of \(^{68}\text{Ga}\)Citrate PET/CT for the detection of PJI in patients without ARMD.

Our study had three main limitations. First, the small study cohort limited the interpretation of the results. This was the first study PET/CT study conducted on ARMD patients, and the planned number of participants was limited due to ethical reasons. The difficulties in recruitment of the planned controls reflected the low prevalence of complications. The current prevalence of revision for mechanical loosening is only 1.4%, and the prevalence of infection in THA patients is 0.5% (Hailier et al., 2015). Second, PET studies of arthroplasty patients (Reinartz et al., 2005; Basu et al., 2014) have used single-modality PET, whereas we applied PET/CT with potential problems due to metal artefacts. Third, we had no readily available reference to interpret the unique uptake of tracer in patients with ARMD. We adopted the Reinartz classification (Reinartz et al., 2005) for the qualitative visual analyses of tracer distribution in periprosthetic areas, which were developed originally for the differentiation of periprosthetic infection and mechanical loosening. This system was not sufficient to describe the characteristic distribution of tracer uptake in ARMD patients, and we chose measurement of the SUV\(_\text{max}\) value of the gluteal muscle region as an additional parameter. SUV\(_\text{max}\) measurements of tracer uptake were undertaken at a distance from the metal components. There was no major uptake of the tracers in the gluteal muscle region in the control patients.

Conclusions

There are four main conclusions to this study. First, the inflammatory pathophysiology of moderate and severe ARMD leads to the high uptake of \(^{18}\text{F}\)FDG in the periprosthetic area. Second, an intraoperative finding of necrosis of the gluteal muscles upon revision surgery was associated with a local increase in \(^{18}\text{F}\)FDG uptake. Third, ARMD patients may show patterns of \(^{18}\text{F}\)FDG and \(^{68}\text{Ga}\)Citrate uptake that are indistinguishable from infection. Lastly, \(^{18}\text{F}\)FDG appears to be sufficient in PET/CT of hip arthroplasty patients with ARMD because there were no cases in which \(^{68}\text{Ga}\)Citrate uptake showed a feature that \(^{18}\text{F}\)FDG did not.

Further prospective studies are needed to examine the value of \(^{68}\text{Ga}\)Citrate PET/CT in the detection of periprosthetic joint infections in arthroplasty patients without ARMD.

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Compliance with ethical standards

The study protocol was approved by our institutional review board.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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