Role of FDG-PET/CT in the evaluation of infectious and inflammatory disease

Pijl, Jordy

DOI:
10.33612/diss.791749362

CHAPTER 10

Importance of blood glucose management before FDG-PET/CT in 322 patients with bacteremia of unknown origin

Jordy P. Pijl, Andor W.J.M. Glaudemans, Olivier Gheysens, Riemer H.J.A. Slart, Thomas C. Kwee

Accepted for publication by the Journal of Nuclear Medicine and Molecular Imaging (April 2023)

ABSTRACT

Purpose
To investigate the effects of blood glucose level on the performance of 2-deoxy-2-(18F) fluoro-D-glucose (18F-FDG) positron emission tomography (PET)/computed tomography (CT) for detecting an infection focus in patients with bacteremia.

Methods
A total of 322 consecutive patients with bacteremia who underwent 18F-FDG PET/CT between 2010 and 2021 were included. Logistic regression analysis was performed to evaluate the association between finding a true positive infection focus on 18F-FDG PET/CT and blood glucose level, type of diabetes, and use of hypoglycemic medication. C-reactive protein (CRP), leukocyte count, duration of antibiotic treatment, and type of isolated bacteria were taken into account as well.

Results
Blood glucose level (OR=0.76 per unit increase, p=<0.001) was significantly and independently associated with 18F-FDG PET/CT outcome. In patients with a blood glucose level between 3.0 and 7.9 mmol/L (54 - 142 mg/dL), the true positive detection rate of 18FFDG PET/CT varied between 61 to 65%, whereas in patients with a blood glucose level between 8.0 and 10.9 mmol/L (144 - 196 mg/dL), the true positive detection rate decreased to 30-38%. In patients with a blood glucose level above 11.0 mmol/L (200 mg/dL), the true positive detection rate was 17%. Besides CRP (OR=1.004 per point increase, p=0.009) no other variables were independently associated with 18F-FDG PET/CT outcome.

Conclusion
In patients with moderate to severe hyperglycemia, 18F-FDG PET/CT was much less likely to identify the focus of infection than in normoglycemic patients. While current guidelines recommend postponing 18F-FDG PET/CT only in case of severe hyperglycemia above 11 mmol/L (200mg/dL), a lower blood glucose threshold seems more appropriate in patients with bacteremia of unknown origin and other infectious diseases.

Key words
Bacteremia, diabetes, 18F-FDG PET/CT, blood glucose, sepsis.

INTRODUCTION

Bacteremia is defined by the presence of viable bacteria in the bloodstream. With an incidence between 100 to 200 cases per 100,000 people per year, bacteremia is one of the most common causes of hospital admission[1,2] As source control is the most important treatment for bacteremia, the mortality rate of bacteremia strongly depends on the ability to locate the source of infection[3]. When no source can be identified, patients are diagnosed with bacteremia of unknown origin[4].

2-deoxy-2-"18Ffluoro-D-glucose"(18F-FDG) PET/CT has proven to be very useful in diagnosing numerous infectious diseases, including infection foci in patients with bacteremia of unknown origin[5,6]. As leukocytes and other inflammatory cells such as cytokines are recruited to infection sites and usually consume more glucose than surrounding tissue, infection foci are often readily visible on 18F-FDG PET/CT[7]. Most bacteria consume glucose themselves as well[8].

Even though glucose metabolism plays a vital role in 18F-FDG PET/CT, the effect of hyperglycemia on the diagnostic performance of 18F-FDG PET/CT remains poorly understood in patients with infectious disease. Theoretically, hyperglycemia can cause reduced cellular 18F-FDG uptake due to direct competition with plasmatic glucose at glucose binding sites[9]. Hyperglycemia can also lead to hyperinsulinemia, which causes upregulation of glucose type 4 transporters and subsequently higher skeletal and myocardial 18F-FDG uptake[10]. Both mechanisms could potentially cause false negative results in hyperglycemic patients with infectious disease, but literature on the clinical consequences of hyperglycemia on the diagnostic accuracy of 18F-FDG PET/CT is limited and conflicting[11-17]. Infection foci may also show a large variation in location and in 18F-FDG avidity. For example, endocarditis may be obscured by physiological high myocardial uptake due to hyperglycemia, and osteomyelitis by just a marginally elevated 18F-FDG uptake compared to the background in low grade infections. Additionally, the prevalence of diabetes mellitus in the community is rapidly increasing, especially in high-income countries[18].

In current PET imaging guidelines, the recommended upper threshold of plasma glucose before performing clinical 18F-FDG PET/CT studies is 11 mmol/L (200 mg/dL)[15-18]. For research studies, an upper glucose threshold of 8.3 mmol/L (150 mg/dL) is recommended (19). While these thresholds are widely applied, the effects of moderate (7.8-10.0 mmol/L or 140-180 mg/dL) to severe hyperglycemia (>10.0 mmol/L or >180 mg/dL) on the diagnostic performance of 18F-FDG PET/CT remain unclear, especially in patients with infectious disease[20].

Therefore, the aim of this study was to assess the effects of hyperglycemia on the diagnostic performance of 18F-FDG PET/CT in patients with bacteremia of unknown origin.

MATERIALS AND METHODS

Study Design and Patients

The electronic patient information system of the University Medical Center Groningen was searched for all patients who underwent 18F-FDG PET/CT for finding the focus of infection between 2010 and 2021 using the keywords 'sepsis', 'bacteremia', 'infection', 'fever', and 'blood culture'.

All patients with bacteremia confirmed by blood cultures taken within two months before 18F-FDG PET/CT were included. Patients with negative blood cultures or blood cultures that were considered contaminated by medical microbiologists were excluded. Follow-up 18FFDG PET/CT scans and 18F-FDG PET/CT scans performed for other reasons than locating the source of infection, such as oncologic follow-up, were excluded as well. The local institutional review board approved this retrospective, single-center study and waived the requirement for written informed consent (Institutional Review Board number 201700145).

Patient Data Review and Reference Standard

The medical files of all patients were reviewed for relevant clinical and biochemical data (age, gender, medical history including presence of diabetes, laboratory values (blood glucose before 18F-FDG PET/CT, CRP, leukocyte count, type of isolated bacteria), duration of hospital stay, use of hypoglycemic medication, antibiotics and immunosuppressive medication, final diagnosis at hospital discharge, and six months follow-up data.

18F-FDG PET/CT Acquisition

All scans were performed using an integrated PET/CT system (Biograph mCT 40 or 64 slice PET/CT or Biograph Vision PET/CT; Siemens, Knoxville, TN, USA) with 3 minutes per bed position.

Low-dose CT was performed for attenuation correction and anatomic mapping with 100 kV and 30 mAs. Data acquisition and reconstruction were in accordance with European Association of Nuclear Medicine/Research 4 Life guidelines[19]. In 60 patients, concomitant full-dose CT of neck, thorax, or abdomen was performed with a constant tube potential of 100 or 120 kV and automatic adjustment of mAs in the z-direction.

Patients fasted for a minimum of 6 hours, and blood glucose concentration was ensured to be less than 11 mmol/L (200 mg/dL) before 3 MBq 18F-FDG/kg body weight was administered intravenously. In 7 patients, 18F-FDG PET/CT was performed even though blood glucose level was above 11 mmol/L due to clinical urgency and poorly manageable diabetes. When there was a clinical suspicion of infective endocarditis, patients were also prepared with a high-fat, low-carbohydrate diet for at least 24 hours. In some patients suspected of endocarditis, a heparin loading dose of 50IU/kg was administered 15 minutes before imaging to reduce myocardial 18F-FDG uptake. PET/CT imaging was performed approximately 60 minutes after intravenous 18F-FDG administration.

18F-FDG PET Interpretation and Reference Standard

18F-FDG PET/CT scans were interpreted by experienced nuclear medicine physicians as part of routine clinical care, using Syngo.Via software (Siemens Healthcare, Erlangen, Germany). All 18F-FDG PET/CT scans were re-evaluated by J.P.P. In case of any doubt or inconsistencies with previous reports and 18F-FDG PET/CT images, the images were re-evaluated by another nuclear medicine physician (A.W.J.M.), who was blinded to original 18F-FDG PET/CT interpretations and all other imaging results, clinical, laboratory, and microbiologic tests.

18F-FDG PET/CT scans showing at least 1 18F-FDG avid lesion localized to an area that did not correspond to physiologic biodistribution of 18F-FDG and did not suggest other pathology than infection, were considered positive for an infection focus. The final clinical diagnosis at hospital discharge was used as a reference standard for 18F-FDG PET/CT results.

This clinical diagnosis was based on all clinically available data including histology or microbiology reports, other imaging results such as ultrasonography or MRI confirming the infection focus found on 18F-FDG PET/CT, and clinical follow-up and treatment outcome for at least six months. The final diagnosis was never based on 18F-FDG PET/CT results alone.

Statistical Analyses

Continuous variables were checked for normal distribution using Shapiro-Wilk tests. Data were presented as mean ± standard deviation or median with interquartile range (IQR) for normally or non-normally distributed data, respectively. Sensitivity, specificity, positive predictive value, and negative predictive value of 18F-FDG PET/CT for detecting an infection focus were calculated, along with 95% confidence intervals (CIs). Age, gender, medical history, medical history including presence of diabetes, laboratory values (blood glucose before 18F-FDG PET/CT, C-reactive protein (CRP), leukocyte count, type of isolated bacteria), duration of hospital stay, and use of hypoglycemic medication, antibiotics and immunosuppressive medication were analyzed with univariable logistic regression as independent variables, and 18F-FDG PET/CT result as the dependent variable. The 18F-FDG PET/CT result was either 'true positive' or 'not true positive' based on the final discharge diagnosis. As such, all true positive results were analyzed against true negative, false positive and false negative results. Corresponding odds ratios (ORs) and 95% CIs were calculated, and P-values less than 0.05 were considered statistically detectable. Variables with a P-value of ≤0.10 on univariable analysis were included in the backward multivariable logistic regression model. All statistical analyses were performed using IBM Statistical Package for the Social Sciences (SPSS) version 28 (SPSS, Chicago, IL, USA).

RESULTS

Patient Population

1389 18F-FDG PET/CT scans from 1209 individual patients were potentially eligible for inclusion. After reviewing the inclusion and exclusion criteria, 322 18F-FDG PET/CT scans from 322 patients were finally included (**Figure 1**). These concerned 206 men and 116 women, with a median age of 63.5 (IQR 20) (**Table 1**). Of these, 66 patients were known to have diabetes type 2 (20%), 7 patients diabetes type 1 (2%), and 4 patients new onset diabetes after transplantation (1%). 54 patients (17%) were using insulin, 27 patients (8%) metformin, and 6 patients (2%) sulfonylurea derivatives. 99 patients (31%) were using immunosuppressive medication such as prednisolone or tacrolimus. The median duration of antibiotic treatment before 18F-FDG PET/CT was 7 days (IQR 7), the median duration between the last positive blood cultures and 18F-FDG PET/CT was 6 days (IQR 7), and the median duration of hospital stay was 23 days (IQR 25). The median CRP level was 87 mg/L (IQR 116), the median leukocyte count 8.9x10^9/L (IQR 6.7), and the median blood glucose level 5.4 mmol/L (IQR 1.8). Most patients had a bacteremia caused by Staphylococcus aureus (30%), followed by gram-negative rods (20%) and Streptococci (14%). The in-hospital mortality rate was 14%.

Table 1 | ***P***atient characteristics

Characteristic	**Value**
Age (years)	63.5 (20)[A]
Gender	
Men	206 (64%)
Women	116 (36%)
Diabetes	
Type 1	7 (2%)
Type 2	66 (20%)
NODAT[B]	4 (1%)
No diabetes	245 (76%)
Use of hypoglycemic medication	
Sulfonylurea derivatives	6 (2%)
Metformin	27 (8%)
Insulin	54 (17%)
None	235 (73%)
Use of immunosuppressive medication	
Yes	99 (31%)
No	223 (69%)
Duration of hospital stay (days)	23 (25)[A]
CRP (mg/L)	87 (116)[A]
Leukocyte count (x10^9/L)	8.9 (6.7)[A]
Blood glucose level (mmol/L)	5.4 (1.8)[A]

Type of isolated bacteria	
Coagulase-negative staphylococci	35 (11%)
Enterococci	38 (12%)
Streptococci	44 (14%)
Gram-negative rods	66 (20%)
S. aureus	97 (30%)
Polymicrobial	31 (10%)
Other	11 (3%)
Duration between last positive blood cultures and 18F-FDG PET/CT (days)	6 (7)[A]
Duration of antibiotic treatment before 18F-FDG PET/CT (days)	7 (7)[A]
Quality of PET image	
Poor	34 (11%)
Reasonable	49 (15%)
Good	239 (74%)
In-hospital mortality	45 (14%)

Notes:

A Median (IQR)

B NODAT = New onset diabetes after transplant

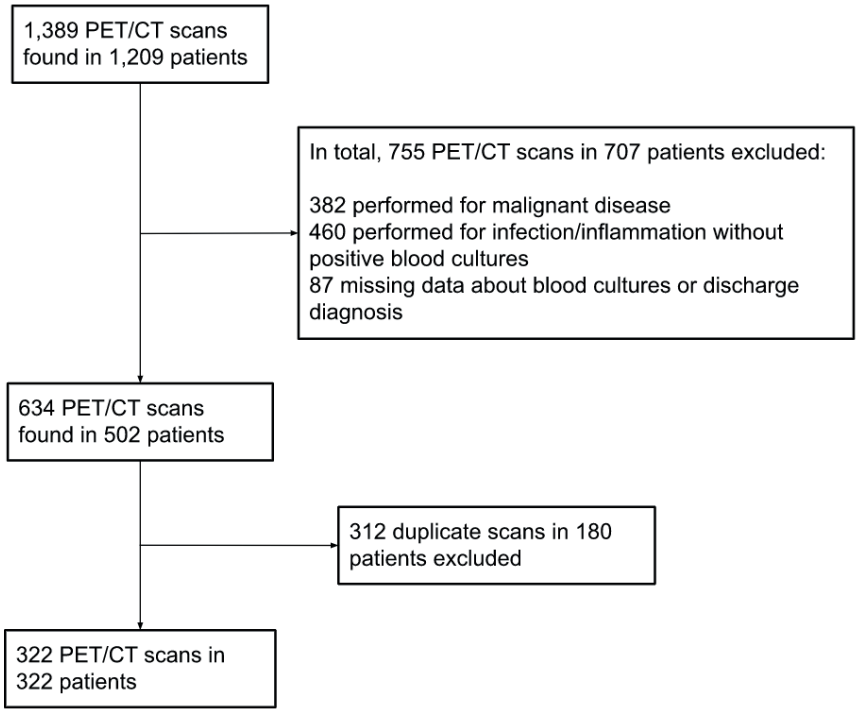

Figure 1 | *Patient inclusion tree*

Diagnostic Performance of 18F-FDG PET/CT

According to the reference standard, 18F-FDG PET/CT yielded 188 true positive results, 19 false positive results, 78 true negative results, and 37 false negative results for finding the infection focus. This resulted in a sensitivity of 83.6%, specificity of 80.4%, positive predictive value of 90.8% and negative predictive value of 67.8% (**Table 2**). The most commonly diagnosed (true positive) infections were spondylodiscitis or sacroiliitis (38 patients, 12%), other musculoskeletal infections such as septic arthritis or osteomyelitis (22 patients, 7%), and pulmonary infections (21 patients 7%) (**Table 3**). The most common false positive diagnoses were 'infected hematoma' shortly after surgery (n=3, 1%), where elevated FDG uptake caused by inflammation was misinterpreted as infection, 'musculoskeletal infection' such as mediastinitis shortly after sternotomy (n=3, 1%), where FDG avidity caused by postoperative changes was misinterpreted as infection, and 'pulmonary infection' (n=3), where 18F-FDG PET/CT mostly showed mildly elevated 18F-FDG uptake of pleural effusion possibly caused by infection, but the final diagnosis was bacteremia of unknown origin. The most common false negative diagnoses included endocarditis (16 patients, 5%) and infected venous access ports (4 patients, 1%) (21).

Table 2 | *Diagnostic performance of 18F-FDG PET/CT for detecting the infection focus*

Statistic	**Value (%)**	**95% CI**
Sensitivity	83.6	78.1 - 88.2
Specificity	80.4	71.1 - 87.8
Positive predictive value	90.8	86.8 - 93.7
Negative predictive value	67.8	60.7 - 74.2

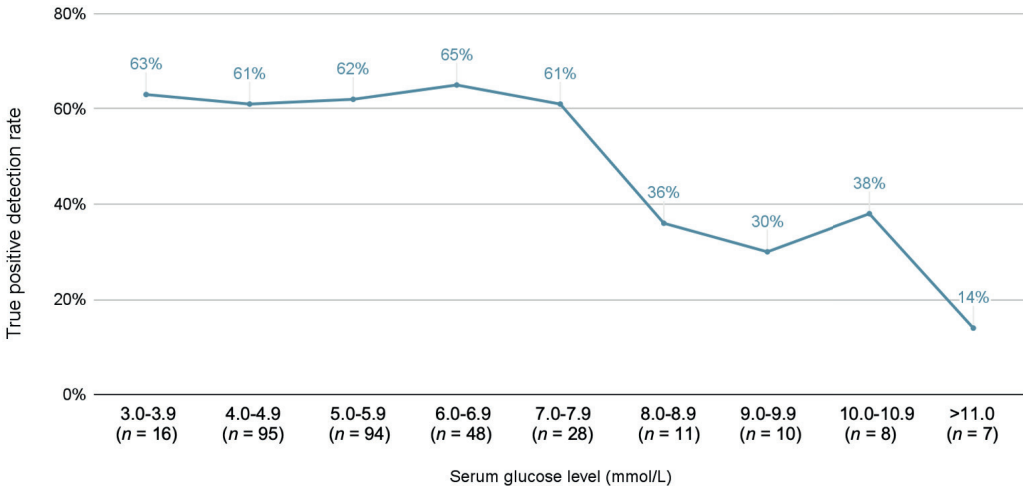

Figure 2 *| Blood glucose level and detection rate of a true positive infection focus on 18F-FDG PET/CT*

Factors Associated with 18F-FDG PET/CT Outcome

On univariable logistic regression, not having diabetes (OR 1.67, p=0.050), CRP (OR=1.003 per unit increase, p=0.003), blood glucose level (OR 0.82 per unit increase, p=0.003), use of immunosuppressants (OR=0.61, p=0.044), and bacteremia caused by enterococci (OR=0.028, p=0.028) were significantly associated with detecting a true positive infection focus on 18FFDG PET/CT (**Table 4**). On multivariable logistic regression, only CRP (OR=1.004 per unit increase, p=0.009) and blood glucose level before 18F-FDG PET/CT (OR=0.76 per unit increase, p=<0.001) remained independently associated with detecting an infection focus on 18F-FDG PET/CT.

In 253 patients with a blood glucose level between 3.0 and 7.9 mmol/L (54 - 142 mg/dL), the true positive detection rate of 18F-FDG PET/CT varied between 61 to 65% (**Figure 2**). In 57 patients with a blood glucose level between 8.0 and 10.9 mmol/L (144 - 196 mg/dL), the true positive detection rate dropped to 30-38%. 18F-FDG PET/CT was performed in 7 patients with a blood glucose level above the recommended threshold of 11.0 mmol/L (200 mg/dL).

In only one of these patients (17%), a true positive infection focus was found. Two exemplary patients are shown in **Figures 3** and **4**.

Table 3 *| True positive, false positive, true negative and false negative infections based on 18F-FDG PET/CT results and final discharge diagnosis*

True positive infections	***n* (188)**	**True negative infections**	***n* (78)**
Central line infection	6 (2%)	Bloodstream infection of unknown origin	63 (20%)
Cyst infection	15 (5%)	Central line infection[A]	7 (2%)
Diffusely disseminated disease	5 (2%)	Infected toe[B]	2 (<1%)
Endocarditis	15 (5%)	Urinary tract infection[C]	6 (2%)
Gastrointestinal infection / abscess	11 (3%)		
Hepatobiliary infection	18 (6%)		
Musculoskeletal infection	22 (7%)		
Pulmonary infection	21 (7%)		
Renal abscess	8 (2%)		
Spondylodiscitis / sacroiliitis	38 (12%)		
Splenic abscess	3 (1%)		
Subcutaneous infection	5 (2%)		
Vascular graft infection	13 (4%)		
Vascular infection	8 (2%)		
False positive infections	***n* (18)**	**False negative infections**	***n* (37)**
Endocarditis	1 (<1%)	Cyst infection	2 (<1%)
Gastro-intestinal	2 (<1%)	Endocarditis	16 (5%)
Infected hematoma after surgery	3 (1%)	Enterocolitis	1 (<1%)
Mediastinitis after sternotomy	1 (<1%)	Cholangitis	3 (1%)
Mucositis	2 (<1%)	Venous access port	4 (1%)
Musculoskeletal	3 (1%)	Mucositis	1 (<1%)
Pulmonary infection	3 (1%)	Parotitis	1 (<1%)
Vascular graft infection	1 (<1%)	Pulmonary infection	2 (<1%)
Vascular infection	2 (<1%)	Renal abscess	4 (1%)
		Vascular infection	3 (1%)

Notes:

A: Central line was already removed before 18F-FDG PET/CT was performed.

B: Patients were only scanned from head-to-femur. Therefore, their legs were not depicted on 18F-FDG PET/CT.

C: These infections were considered true negative as well, as 18F-FDG excretion through the urinary tract masks urinary tract infections.

Effect of Hypoglycemic Medication Use on 18F-FDG PET/CT Outcome

On univariable logistic regression, only use of metformin approached statistical significance (OR=0.48, p=0.077). Use of insulin (OR=0.71, p=0.26) or sulfonylurea derivatives (OR=2.11, p=0.52) were not significantly associated with 18F-FDG PET/CT outcome. The individual dosages were not specifically analyzed.

***Table 4** | Factors associated with detecting a true-positive infection focus on 18F-FDG PET/CT*

Factor	Univariable OR (95% CI)	p	Multivariable OR (95% CI)	p
Clinical				
Age	1.0 (0.99-1.01)	0.99		
Male gender	0.72 (0.45-1.15)	0.17		
Diabetes type 1	0.93 (0.20-4.22)	0.92		
Diabetes type 2	0.61 (0.36-1.03)	0.076		
No diabetes	1.67 (0.99-2.81)	0.050		
Duration of hospital stay	1.0 (0.99-1.00)	0.44		
Laboratory values				
CRP	1.004 (1.002-1.007)	0.003	1.004 (1.001-1.007)	0.009
Leukocyte count	1.01 (0.98-1.04)	0.64		
Blood glucose level	0.82 (0.72-0.93)	0.003	0.76 (0.65-0.89)	<0.001
Medication use				
Immunosuppressives	0.61 (0.38-0.99)	0.044		
Sulfonylurea derivatives	0.93 (0.20-4.22)	0.92		
Metformin	0.48 (0.21-1.08)	0.077		
Insulin	0.71 (0.39-1.29)	0.26		
Days of antibiotic treatment	0.99 (0.97-1.01)	0.25		
Microbiology				
Coagulase-negative staphylococci (*n* = 35)	0.62 (0.31-1.26)	0.19		
Enterococci (*n* =3 8)	0.45 (0.23-0.92)	0.028		
Streptococci (*n* = 44)	1.13 (0.59-2.16)	0.72		
Gram-negative rods (*n* = 66)	1.51 (0.86-2.67)	0.15		
S. aureus (*n* = 97)	1.24 (0.76-2.02)	0.40		
Polymicrobial (*n* = 31)	0.96 (0.45-2.04)	0.91		
Other (*n* = 11)	1.23 (0.35-4.28)	0.75		

DISCUSSION

The results of this study show that management of blood glucose before performing 18FFDG PET/CT has a large impact on its ability to identify the infection focus in patients with bacteremia of unknown origin.

On univariable and multivariable logistic regression, a higher blood glucose was significantly associated with a lower odds of detecting an infection focus on 18F-FDG PET/CT (OR=0.76, p=0.003). The detection rate of 18F-FDG PET/CT was 60-65% in patients with a blood glucose level below 8.0 mmol/L (144 mg/dL), but declined to 14-38% in patients with a blood glucose level above 8.0 mmol/L.

Most nuclear imaging guidelines recommend an upper glucose threshold of 11 mmol/L (200 mg/dL) before 18F-FDG PET/CT should be postponed[22]. However, this also depends on the indication for 18F-FDG PET/CT and the setting in which 18F-FDG PET/CT is performed.

For example, the recommended upper threshold for brain imaging is 8.8 mmol/L (160 mg/dL), and the European Association for Nuclear Medicine recommends an upper threshold of 7.0-8.3

mmol/L (126-150 mg/dL) for clinical trials[16]. The procedure guideline for tumor imaging from the Society of Nuclear Medicine recommends an upper threshold between 8.3-11 mmol/L (150-200 mg/dL)[23]. The rationale behind these differences in upper threshold is unclear. Also, there is no distinction between glucose threshold in patients who undergo 18F-FDG PET/CT for oncologic disease and infectious disease, even though the physiology behind elevated 18F-FDG uptake in oncologic and infectious lesions is different. Cancer cells consume much glucose due to increased proliferation and inefficient metabolism with glycolysis instead of oxidative phosphorylation as their main metabolic pathway[24]. An infection focus is mainly thought to be 18F-FDG avid mainly due to recruitment of other metabolically active cells such as granulocytes. Additionally, most bacteria also consume glucose, and therefore, 18F-FDG. As the 18F-FDG avidity of different types of bacteria also differs, it could be hypothesized that 18F-FDG uptake of infection foci with more fulminant bacteria, such as S. aureus, are less easily affected by high blood glucose levels than less fulminant pathogens[8]. On univariable regression, an Enterococcus bacteremia was also significantly associated with a lower odds of identifying an infection focus on 18F-FDG PET/CT (OR=0.45, p=0.028). However, statistical significance of this variable was not maintained in the multivariate model.

In both cancer and infectious disease, high blood glucose can cause reduced cellular 18FFDG uptake due to direct competition with plasmatic glucose at glucose binding sites and upregulation of glucose transporters of other tissues resulting in a lower lesion-tobackground ratio[9]. Some studies also suggest that cancer cells are less easily saturated by glucose than other tissues[14, 25].

Not having diabetes was significantly associated with identifying an infection focus on 18FFDG PET/CT on univariable logistic regression (OR 1.67, p=0.050), but not on multivariable logistic regression. This suggests that diabetic patients may not be at a disadvantage in having their infection focus detected on 18F-FDG PET/CT when their blood glucose is properly managed. This includes fasting for 4-6 hours, while also making sure no external glucose is intravenously administered. Rapid-acting insulin should only be administered up to 4 hours before 18F-FDG PET/CT, short-acting insulin within 6 hours, and intermediate or long-acting insulin should not be used on the day 18F-FDG PET/CT is scheduled[26].

Interestingly, use of hypoglycemic medication such as metformin or insulin was not statistically associated with 18F-FDG PET/CT outcome. This implies that a satisfactory effect of these medications on glucose level, but not use of these medications itself, is important for 18F-FDG PET/CT outcome.

Besides blood glucose, CRP was the only other factor independently associated with 18FFDG PET/CT outcome. This is in line with previous studies, which also found that a higher CRP increases the chance of identifying an infection focus on 18F-FDG PET/CT in patients with bacteremia[27–29]. Although a previous study of our own (Pijl et al, 2019) showed a statistically detectable relation between duration of antibiotic use and 18F-FDG PET/CT outcome, this relation was not shown in our current study (OR=0.99 per day, p=0.25). This may be due to including much more recent patients in the current study, while our hospital became more selective in only providing specialized tertiary care over the past years. This 142 resulted in

inclusion of more patients with comorbidity such as infected vascular grafts or prostheses requiring chronic antibiotic suppressive therapy, or immunocompromised patients requiring prophylactic antibiotic treatment.

Previous literature on the effects of hyperglycemia on 18F-FDG PET/CT outcome in patients with infectious disease is limited. In a study by Rabkin et al, 123 patients with infection or inflammation were included[12]. 19 patients had a glucose level above 10 mmol/L (180 mg/dL), and in 11 patients (58%) a true positive infection or inflammation focus was found. No statistically detectable difference was found in the number of false negative results between normoglycemic and hyperglycemic patients. Because patients with both inflammatory and infectious disease were included, it is unclear how many of these 11 patients were suffering from infectious disease. Additionally, not all patients had an infection of unknown origin. 26 out of 123 patients (21%) underwent 18F-FDG PET/CT to evaluate their diabetic foot. As these patients are more likely to have hyperglycemia than general patients with bacteremia of unknown origin, and the a priori chance of detecting an infection in patients with a chronic wound such as diabetic foot is likely higher than in all patients with bacteremia of unknown origin, this could have led to a higher number of true positive results in hyperglycemic patients than in our patient population[12].

In a large meta-analysis by Eskian et al, conducted to evaluate the effect of pre-scan blood glucose levels on standard uptake values (SUV) of healthy tissue, 8380 patients were included with SUV measurements of the liver, brain, muscle, blood pool, or tumors[14]. Patients were categorized in five groups based on blood glucose: <109 mg/dL (euglycemic), 110-125 mg/dL (mild hyperglycemia), 126-150 mg/dL (moderate hyperglycemia), 151-200 mg/dL (high moderate hyperglycemia), and >200 mg/dL (severe hyperglycemia). Eskian et al concluded that blood glucose only affected 18F-FDG uptake of tumors above a glucose level of 11 mmol/L (200 mg/dL). Blood glucose showed a statistically detectable negative correlation with 18F-FDG uptake in muscle and brain in all hyperglycemic groups, and a statistically detectable positive correlation in all hyperglycemic patients with 18F-FDG uptake in the blood pool and liver. Unfortunately, patients with infectious disease were not included, while the underlying mechanism of 18F-FDG avidity for infectious and oncologic lesions is different.

Our study was compromised by some limitations. First, due to the retrospective nature of this study, selection bias may have occurred. While all patients were selected using objective criteria, not all patients from our hospital with bacteremia underwent 18F-FDG PET/CT as this indication was set by the treating physician. Second, the reference standard for 18F-FDG PET/CT, namely the clinical diagnosis at hospital discharge, was suboptimal as this diagnosis also included 18F-FDG PET/CT results. However, this diagnosis was never based on 18F-FDG PET/CT results alone. For future research, it would be interesting to conduct quantitative measurements of infection foci in patients with bacteremia to examine whether moderate to severe hyperglycemia may not only result in a lower detection rate of 18F-FDG PET/CT, but also in lower 18F-FDG uptake of infection foci compared to normoglycemic patients. The 143 difference in 18F-FDG avidity of infections caused by different types of bacteria (e.g. Enterococci versus S. aureus) could be investigated as well.

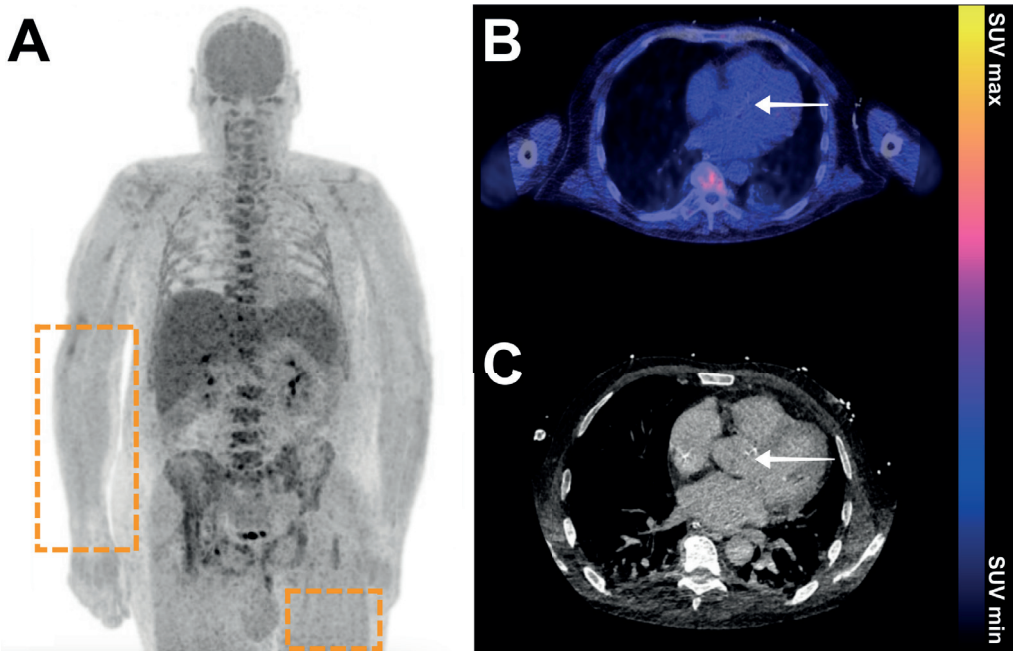

***Figure 3* |**

A 64-year-old man presented to the hospital with septic shock. His medical history showed diabetes mellitus type 2, hypertension, and a myocardial infarction. At presentation, his CRP level was 78 mg/L and his leukocyte count was $13.3x10^9$/L. Blood cultures were positive for *Staphylococcus aureus*. To identify the focus of infection, 18F-FDG PET/CT was performed. Before 18F-FDG PET/CT, his blood glucose level measured 11.1 mmol/L (200 mg/dL). Coronal maximum intensity projection 18F-FDG PET (A) showed diffusely increased 18F-FDG uptake of skeletal muscle (orange dashed rectangles), which made the images difficult to interpret. The high glucose level was deemed the most probable cause for this elevated skeletal muscle uptake. Fused axial 18F-FDG PET/CT and low-dose CT did not show elevated 18F-FDG uptake at the aortic valve (B and C, white arrow), even though a valvular vegetation of the aortic valve was seen on transesophageal ultrasound, suggestive of endocarditis. Thus, the 18F-FDG PET/CT result was deemed false negative. Despite antibiotic treatment, the patient died several days after 18F-FDG PET/CT was performed. Autopsy was not performed.

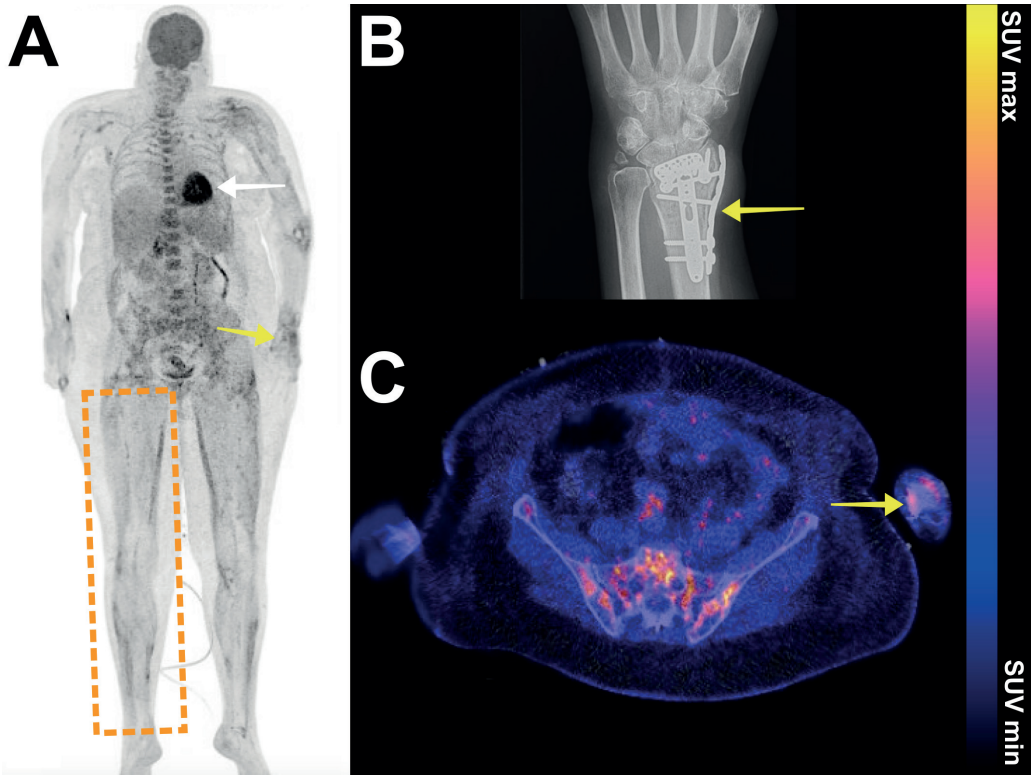

Figure 4 **|**
A 64-year-old woman presented to the hospital with a painful left wrist and fever. Her medical history showed a bilateral hip replacement and internal fixation of a left wrist fracture with plates and screws earlier that year. On admittance, she had a CRP of 274 mg/L and leukocyte count of 18.4x10^9/L. Blood cultures were positive for *Staphylococcus aureus*. 18F-FDG PET/CT was performed to identify the primary infection focus and potential metastatic foci. By accident, insulin was administered to the patient shortly before 18F-FDG PET/CT was performed. Coronal maximum intensity projection showed diffusely increased 18F-FDG uptake of skeletal muscle (A, orange dashed rectangle), rendering the 18F-FDG PET images difficult to interpret. The myocardium also showed elevated 18F-FDG uptake (A, white arrow). Pathologic 18F-FDG uptake was seen at the left wrist (A, yellow arrow), which was interpreted as infected osteosynthetic material of the left wrist (B, yellow arrow), also visible on axial fused 18F-FDG PET/CT (C, yellow arrow). The plates and screws of the left wrist were surgically removed and cultured. These cultures were also positive for Staphylococcus aureus. Despite antibiotic treatment, the patient died one week after performing 18F-FDG PET/CT due to septic shock.

CONCLUSION

In patients with bacteremia with a glucose level above 8 mmol/L (144 mg/dL), 18F-FDG PET/CT was much less likely to identify the infection focus. While current guidelines recommend postponing 18F-FDG PET/CT only in case of severe hyperglycemia above 11 mmol/L (200mg/dL), the diagnostic power of 18F-FDG PET/CT already seems affected in patients with only moderate hyperglycemia (above 8.0 mmol/L or 144 mg/dL). Stricter blood glucose management seems appropriate in patients who undergo 18F-FDG PET/CT for bacteremia of unknown origin or other infectious diseases. Diabetic patients with adequately controlled blood glucose levels had similar detection rates on 18F-FDG PET/CT compared to non-diabetic patients.

DISCLOSURE

All authors report no conflict of interest.

Key points

Question: Does moderate hyperglycemia affect the ability of 18F-FDG PET/CT to find the infection focus in patients with bacteremia of unknown origin?

Pertinent findings: In our study including 322 patients, the true positive detection rate of 18F-FDG PET/CT varied between 61 to 65% in patients with a blood glucose level between 3.0 and 7.9 mmol/L (54 - 142 mg/dL). In patients with a blood glucose level between 8.0 and 10.9 mmol/L (144 - 196 mg/dL), the true positive detection rate decreased to 30-38%. In patients with a blood glucose level above 11.0 mmol/L (200 mg/dL), the true positive detection rate was 17%.

Implications for patient care: Nuclear medicine should be aware that even only moderate hyperglycemia already negatively affects 18F-FDG PET/CT's ability to locate the source of infection in patients with bacteremia of unknown origin. This may warrant adjustment of current scanning protocols, where an upper pre-scan blood glucose threshold of 11.0 mmol/L (200 mg/dL) is generally maintained.

REFERENCES

1 Laupland KB. Incidence of bloodstream infection: a review of population-based studies. Clin Microbiol Infect. 2013;19:492–500.
2 Anderson DJ, Moehring RW, Sloane R, Schmader KE, Weber DJ, et al. Bloodstream infections in community hospitals in the 21st century: a multicenter cohort study. PLoS One. 2014;9:e91713.
3 Tabah A, Koulenti D, Laupland K, Misset B, Valles J, et al. Characteristics and determinants of outcome of hospital-acquired bloodstream infections in intensive care units: the EUROBACT International Cohort Study. Intensive Care Med. 2012;38:1930–1945.
4 Courjon J, Demonchy E, Degand N, Risso K, Ruimy R, et al. Patients with communityacquired bacteremia of unknown origin: clinical characteristics and usefulness of microbiological results for therapeutic issues: a single-center cohort study. Ann Clin Microbiol Antimicrob. 2017;16:40.
5 Kung BT, Seraj SM, Zadeh MZ, Rojulpote C, Kothekar E et al. An update on the role of F-18F-FDG PET/CT in major infectious and inflammatory diseases. Am J Nucl Med Mol Imaging. 2019;9:255–273.
6 Hess S, Hansson SH, Pedersen KT, Basu S, Høilund-Carlsen PF. 18F-FDG PET/CT in infectious and inflammatory iseases. PET Clin. 2014;9:497–519,vi–vii.
7 Vos FJ, Bleeker-Rovers CP, Sturm PD, Krabbe PFM, van Dijk APJ, et al. 18F-18F-FDG PET/CT for detection of metastatic infection in gram-positive bacteremia. J Nucl Med. 2010;51:1234–1240.
8 Heuker M, Sijbesma JWA, Aguilar Suárez R, de Jong JR, Boersma HH, et al. In vitro imaging of bacteria using F-fluorodeoxyglucose micro positron emission tomography. Sci Rep. 2017;7:4973.
9 Finessi M, Bisi G, Deandreis D. Hyperglycemia and 18F-18F-FDG PET/CT, issues and problem solving: a literature review. Acta Diabetol. 2020;57:253–262.
10 Shao D, Tian R. Glucose transporters in cardiac metabolism and hypertrophy. Compr Physiol. 2015;6:331–351.
11 Hess S, Scholtens AM, Gormsen LC. Patient preparation and patient-related challenges with 18F-FDG PET/CT in infectious and inflammatory disease. PET Clin. 2020;15:125–134.
12 Rabkin Z, Israel O, Keidar Z. Do hyperglycemia and diabetes affect the incidence of false-negative 18F-18F-FDG PET/CT studies in patients evaluated for infection or inflammation and cancer? A Comparative analysis. J Nucl Med. 2010;51:1015–1020.
13 Zhao S, Kuge Y, Tsukamoto E, Mochizuki T, Kato T, Hikosaka K, et al. Effects of insulin and glucose loading on 18F-FDG uptake in experimental malignant tumours and inflammatory lesions. Eur J Nucl Med. 2001;28:730–735.
14 Eskian M, Alavi A, Khorasanizadeh M, Viglianti BL, Jacobsson H, et al. Effect of blood glucose level on standardized uptake value (SUV) in F- 18F-FDG PET-scan: a systematic review and meta-analysis of 20,807 individual SUV measurements. Eur J Nucl Med Mol Imaging. 2019;46:224–237.
15 Yang H, Zhuang H, Rubello D, Alavi A. Mild-to-moderate hyperglycemia will not decrease the sensitivity of 18F-18F-FDG PET imaging in the detection of pedal osteomyelitis in diabetic patients. Nuclear Medicine Communications. 2016; 37(3):259-62.
16 Sprinz C, Altmayer S, Zanon M, Watte G, Irion K, et al. Effects of blood glucose level on 18F-18F-FDG uptake for PET/CT in normal organs: A systematic review. PLoS One. 2018;13: e0193140.
17 Slart RHJA, Glaudemans AWJM, Gheysens O, Lubberink M, Kero T, et al. Procedural recommendations of cardiac PET/CT imaging: standardization in inflammatory-, infective-, infiltrative-, and innervation (4Is)-related cardiovascular diseases: a joint collaboration of the EACVI and the EANM. Eur J Nucl Med Mol Imaging. 2021;48:1016–1039.

18 Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9 edition. Diabetes Res Clin Pract. 2019;157:107843.
19 Boellaard R, Delgado-Bolton R, Oyen WJG, Giammarile F, Tatsch K, et al. 18F-FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0. Eur J Nucl Med Mol Imaging. 2015;42:328–354.
20 Qureshi AI, Huang W, Lobanova I, Chandrasekaran PN, Hanley DF, et al. Effect of moderate and severe persistent hyperglycemia on outcomes in patients with intracerebral hemorrhage. Stroke. 2022;53:1226–1234.
21 Li JS, Sexton DJ, Mick N, Nettles R, Fowler VG Jr, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis. 2000;30:633–638.
22 Dudoignon D, Pattison DA, Legallois D, Hicks RJ, Aide N. The utility of pharmacological and radiological interventions to optimize diagnostic information from PET/CT. Cancer Imaging. 2020;20:68.
23 Delbeke D, Coleman RE, Guiberteau MJ, Brown ML, Royal HD, al. Procedure guideline for tumor imaging with 18F-18F-FDG PET/CT 1.0. J Nucl Med. 2006;47:885–895.
24 Yu L, Chen X, Sun X, Wang L, Chen S. The glycolytic switch in tumors: how many players are involved? J Cancer. 2017;8:3430–3440.
25 Gorenberg M, Hallett WA, O'Doherty MJ. Does diabetes affect ((18)F)18F-FDG standardised uptake values in lung cancer? Eur J Nucl Med Mol Imaging. 2002;29:1324–1327.
26 Evangelista L, Gori S, Rubini G, Gallo M. Management of hyperglycemia in oncological patients scheduled for an 18F-FDG PET/CT examination. Clinical and Translational Imaging. 2019;7:447–450.
27 Pijl JP, Kwee TC, Slart RHJA, Yakar D, Wouthuyzen-Bakker M, Glaudemans AWJM. Clinical implications of increased uptake in bone marrow and spleen on 18F-FDG PET in patients with bacteremia. Eur J Nucl Med Mol Imaging. 2021;48:1467–1477.
28 Tsai H-Y, Lee M-H, Wan C-H, Yang L-Y, Yen T-C, et al. C-reactive protein levels can predict positive F-18F-FDG PET/CT findings that lead to management changes in patients with bacteremia. J Microbiol Immunol Infect. 2018;51:839–846.
29 Okuyucu K, Alagoz E, Demirbas S, Ince S, Karakas A, et al. Evaluation of predictor variables of diagnostic (18F) 18F-FDG PET/CT in fever of unknown origin. Q J Nucl Med Mol Imaging. 2018;62: 313–320.