



Management of hyperglycemia in oncological patients scheduled for an FDG-PET/CT examination

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Positron-emission tomography combined with X-ray computed tomography and using [¹⁸F]-fluorodeoxyglucose (FDG-PET/CT) is being used for staging, restaging, follow-up, and treatment monitoring of several glucose avid tumors. Since FDG and glucose compete for the same transporters and for hexokinase, hyperglycemia may significantly modify the value of the semi-quantitative variables commonly used for estimating the uptake of FDG, including the standardized uptake value (SUV). Therefore, this issue is of particular relevance, when FDG-PET/CT is used in patients with poorly controlled diabetes mellitus. Thus, because of the competition between FDG and glucose, the control of glycemia may be relevant when imaging is being pursued, with the use of SUV, to estimate the degree of malignancy during the staging of the tumor and in particular for the comparison during follow-up and in case of therapy monitoring. Indeed this issue has been considered, since PET with FDG was in the early phase of introduction into clinical practice about 40 years ago.

In spite of the acknowledgement of this very relevant issue, demonstrated by a simple PubMed search using the

terms “FDG PET” and “blood glucose levels” and “FDG PET” and “hyperglycemia” that allowed to retrieve more than 200 articles, there is only a limited number of papers dealing with the practical procedure to be used in case of hyperglycemia in oncological patients undergoing an FDG-PET/CT examination.

The aim of this paper is to provide a practical guidance for the management of hyperglycemia, either due to diabetes mellitus or other causes, in oncological patients scheduled for FDG PET/CT, to optimize the preparation for the exam and increase the reliability of the semi-quantitative assessment of FDG uptake in tumor.

The Society of Nuclear Medicine and Molecular Imaging (SNMMI) guidelines recommend rescheduling of the scan when glycemia is above 150–200 mg/dL [1]. The European Association of Nuclear Medicine and Molecular Imaging (EANMMI) guidelines suggest that FDG PET/CT study should be rescheduled, if glycemia is higher than or equal to 200 mg/dL [2]. Both guidelines suggest that pre-scan hyperglycemia may be reduced by administration of rapid-acting insulin. However, the EANM guidelines consider also the impact of longer acting insulin and recommend specific time intervals for the administration of the different types of insulin prior to scan. The inconsistency between different guidelines, which originates from lack of robust and credible evidence, has resulted in a diverse range of accepted pre-scan glycemia levels in clinical PET imaging. In a web-based survey of PET/CT users, specialists from 128 PET centers worldwide responded to the question regarding the pre-scan glycemia cutoff used at their institutes [3]. Cutoff values varied from 150 to 250 mg/dL (8.3–13.9 mmol/L) and 7% of the sites used no cutoff. Based on the recent systematic review and meta-analysis by Eskian et al. [4], patients who are still hyperglycemic after at least 4 h of fasting would have significantly lower FDG uptake in the brain and muscles and significantly higher FDG uptake in the liver and mediastinal blood pool in comparison with euglycemic patients. However, pooled findings reported that glycemia levels

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do not have any apparent significant effect on FDG uptake by tumors. Considering the lack of significant correlation between glycemia and FDG uptake in tumors, Eskian et al. recommend no interventions for hyperglycemic patients who are scheduled to undergo PET scan, except under two conditions: glycemia > 200 mg/dL, or when the liver is the area of interest [4]. In this latter condition, FDG uptake significantly increases in liver during hyperglycemia, therefore patients should be kept euglycemic (glycemia \leq 110 mg/dL), when liver assessment is required, to prevent decreased tumor-to-background uptake ratios.

There are other important issues about the management of patients with diabetes and who are scheduled to undergo PET/CT scan for oncological requests. First, pre-hydration is important to favor the elimination of FDG in the bladder, to reduce artifacts and for radiation safety reasons, the consumption of 1 L of water in the 2 h preceding the FDG administration is recommended, regardless of the presence of diabetes. Second, any infusion used for intravenous pre-hydration should not contain glucose.

By taking into account the most recent papers dealing with this issue, based on large number of patients (Table 1) and the guidelines issued by the SNMMI, as well as those of the EANMMI, some frequently asked questions are addressed below.

1. What is the acceptable glycemia for FDG-PET/CT scan?

In case of total body FDG PET/CT examination, glycemia should be lower than 200 mg/dL; if higher, the FDG-PET/CT study should be rescheduled; otherwise, specific interventions should be implemented to lower the glycemia levels. However, the current recommendation for brain PET/CT is to limit FDG administration to patients with glycemia < 160 mg/dL [5]. It has been demonstrated that brain imaging in healthy volunteers

with hyperglycemia may reveal patterns that are similar to those found in neurodegenerative diseases [6].

2. What is the correct preparation before an FDG-PET/CT scan in patients with diabetes treated with anti-diabetic agents other than insulin?

In patients with type 2 diabetes treated with oral anti-diabetic agents, FDG-PET/CT should preferably be performed late in the morning. Moreover, to reduce the cross reaction with the intravenous contrast agent and the physiological uptake of FDG in the bowel, metformin should be discontinued at least 48 h before the procedure [7], especially in patients with a suspected or known malignant abdominal disease. No evidence is available about sulfonilureas, glinides, alpha-glucosidase inhibitors, DPP-4 inhibitors, SGLT2-inhibitors, and GLP-1 receptor agonists, whereas preliminary evidence suggests that pioglitazone may have increased the uptake of FDG by malignant lesions [8].

3. What is the correct preparation before an FDG-PET/CT scan in patients with diabetes treated with insulin?

In patients with type 1 diabetes, as well as in patients with type 2 diabetes treated with insulin, an FDG-PET/CT study can be scheduled at different hours of the day, suggesting different approaches for the preparation:

- a. In case of FDG-PET/CT performed early in the morning, particular attention should be given to the type of insulin. In case of long-acting insulin administered the evening before the exam, there might be a slight interference with the FDG-PET/CT study. Thus, if early morning is the preferred time for the examination, intermediate-acting (instead of long-acting) insulin should be recommended the day before the examination. Thereafter, these patients should have a normal breakfast and restart with the daily amount of insulin.

Table 1 Selected studies about hyperglycemia and FDG PET/CT examination

References	Year of publication	Type of article	No. of pts	Outcome of interest
Kaneta et al. [10]	2006	Original article	159	The influence of fasting and hyperglycemia on myocardial FDG uptake
Janseen et al. [11]	2010	Original article	30	The impact of glycemia on PET-based treatment response prediction in rectal cancer
Kubota et al. [12]	2011	Original article	70	The effect of glycemia on FDG liver uptake
Lindholm et al. [13]	2013	Original article	500	The influence of glycemia on the FDG uptake in normal organs
Niccoli-Asabella et al. [14]	2013	Review	13,063	The screening at the preliminary visit and a subsequent good preparation of the patient before scheduling can reduce hyperglycemic status
Khandani et al. [15]	2016	Original article	117	The frequency of glycemia > 150 mg/dL in patients without diabetes
Sprintz et al. [16]	2017	Review	2714	The influence of glycemia on the FDG uptake in normal organs
Sprintz et al. [17]	2018	Original article	5623	The influence of glycemia on the FDG uptake in normal organs
Eskian et al. [4]	2019	Review	20,807	To evaluate the effect of glycemia on SUV (standardized uptake value)

b. In case of FDG-PET/CT performed late in the morning or at mid-day, the patient should have a normal breakfast early in the morning (around 7.00 a.m.) and receive the usual dose of insulin. FDG should be administered at least 4 h after the subcutaneous injection of rapid-acting insulin or 6 h after the subcutaneous injection of usual short-acting insulin. An FDG-PET/CT study should not be performed on the same day of the administration of intermediate-acting and/or long-acting insulin.

4. How to manage patients treated with continuous insulin infusion?

In patients treated with continuous insulin infusion, FDG PET/CT scan should be scheduled early in the morning. The insulin pump should be switched off at least 4 h before FDG administration. The patient can have breakfast after the FDG PET/CT study and restart the continuous insulin infusion.

5. What is the correct preparation before an FDG-PET/CT scan in patients with diabetes on artificial nutrition?

Both parenteral nutrition and intravenous administration of fluids containing glucose should be discontinued at least 4 h before FDG administration.

6. How to manage a patient with diabetes and with a glycemia > 200 mg/dL?

Reduction of glycemia by administration of rapid-acting insulin can be considered, but FDG-PET/CT study could also be postponed depending on the type and route of insulin administration. Unnecessary interventions aimed at lowering glycemia are sometimes both time and resources consuming, including insulin injection, also with a potential decrease of PET/CT scan sensitivity due to a greater muscle uptake of FDG [9]. Therefore, the examination should be postponed, whenever possible. However, some procedures can be adopted:

- The patient should be asked to walk and to hydrate, rechecking glycemia periodically until an acceptable level has been achieved;

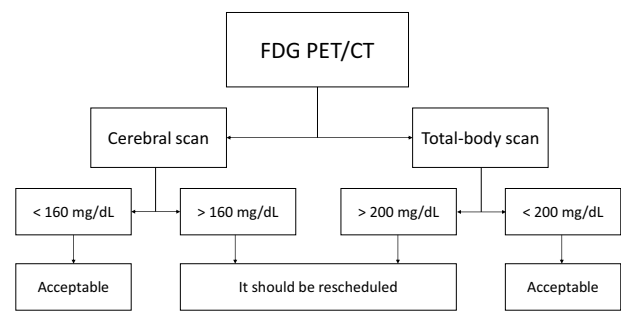


Fig. 1 A flow chart for the management of patients candidates to FDG PET/CT scan, in accordance with glycemia levels

- A subcutaneous injection of a rapid-acting insulin should be preferred, while regular insulin, intermediate-acting, or long-acting insulin are not recommended.

7. How to manage patients with drug-induced or tumor-induced hyperglycemia?

Drug and tumor-induced hyperglycemia should be managed as previously reported, rescheduling the scan or administering rapid-acting insulin. The withdrawal of treatments (e.g., corticosteroids and chemotherapy) should be avoided and a discussion with the oncologist and diabetologist is strongly recommended. The above-mentioned concepts are summarized in Fig. 1 and Table 2.

Conclusions

The measurement of glycemia before an FDG-PET/CT procedure is key for a good quality of the examination, thus, to balance the clinical needs and the quality of images, carefully selected strategies, tailored for each patient, should be sought.

Table 2 Scheduled times for FDG PET/CT exams in diabetic patients

Time	Oral anti-diabetic agents	Insulin
Early morning	Not recommended	1. An intermediate insulin is recommended the day before exam 2. In case of continuous infusion, it should be stopped 4 h before
Late morning	Recommended ^a	A short-acting insulin is preferred

^aIn case of metformin, it should be withdrawal 48 h before examination

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Human and animal rights This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study informed consent is not required.

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