



## MANAGEMENT OF BLOOD GLUCOSE LEVELS IN ONCOLOGICAL PATIENTS SCHEDULED FOR FDG PET/CT EXAMINATION

**AIMN (Laura Evangelista<sup>1</sup> and Giuseppe Rubini<sup>2</sup>), AMD (Marco Gallo<sup>3</sup>), AIOM (Stefania Gori<sup>4</sup>), on behalf of the 'Diabetes and Cancer' working group<sup>5</sup>**

<sup>1</sup>Nuclear Medicine Unit, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy

<sup>2</sup>Nuclear Medicine Unit, University of Bari "Aldo Moro", Bari, Italy

<sup>3</sup>Oncological Endocrinology Unit, Department of Medical Sciences, University of Turin, AOU Città della Salute e della Scienza di Torino, Turin, Italy

<sup>4</sup>Oncology Department, IRCCS Sacro Cuore Don Calabria, Negrar, Verona, Italy

<sup>5</sup>See Appendix

Positron-emission tomography (PET) is a nuclear medicine functional imaging technique that is used for routine clinical oncology to confirm a tumour diagnosis, verify the presence of metastases or evaluate treatment effects. The most commonly used is fluorodeoxyglucose (FDG) PET, whose results may be falsely altered in the presence of high blood glucose levels, such as in patients with poorly controlled diabetes mellitus. The aim of this consensus document is to provide a practical guidance for the management of glucose control in oncological patients scheduled for FDG PET examination, in order to optimize the preparation for the exam and increase the reliability of its results.

Prescan blood glucose level (BGL) influences tissue FDG uptake, in particular hyperglycaemia during FDG-PET scan may decrease the sensitivity for the detection of malignant tissue (1). Searching the terms "FDG PET" AND "blood glucose levels" more than 200 articles were retrieved on PubMed. However, the majority of them do not regard the management of BGL in oncological patients. Moreover, most of them had been published more than 15 years ago. Therefore, in order to provide an updated information about the management of oncological patients with high glucose levels before PET/CT scan, we have considered only some studies. The most useful ones are reported in *Table 1*.

**Table 1.** Selected studies about hyperglycaemia and FDG PET/CT examination.

Authors, ref	Year of pub	Type of article	N. pts	Outcome of interest
Kaneta et al. (2)	2006	Original article	159	Myocardial FDG uptake
Janseen et al. (3)	2010	Original article	30	The impact of BGL on PET-based treatment response prediction in rectal cancer
Kubota et al. (4)	2011	Original article	70	The effect of BGL on FDG liver uptake
Lindholm et al. (5)	2013	Original article	500	The influence of BGL on the FDG uptake in normal organs
Niccoli-Asabella et al. (6)	2013	Review	13,063	The screening at the preliminary visit and a subsequent good preparation of the patient before scheduling can reduce hyperglycaemic status

Khandani et al. (7)	2016	Original article	117	The frequency of BGL > 150 mg/dL in patients without diabetes
Sprintz et al. (8)	2017	Review	2,714	The influence of BGL on the FDG uptake in normal organs
Sprintz et al. (9)	2018	Original article	5,623	The influence of BGL on the FDG uptake in normal organs
Eskian et al. (10)	2019	Review	20,807	To evaluate the effect of BGL on SUV (Standardized Uptake Value)

Furthermore, we have considered the recommendations provided by the most widespread nuclear medicine clinical guidelines, such as the American (11) and European (12) Guidelines. The Society of Nuclear Medicine and Molecular Imaging (SNMMI) Guidelines (11) recommend rescheduling the scan if BGL is greater than a range of 150–200 mg/dL. The European Association of Nuclear Medicine (EANM) Guidelines (12) suggest that the FDG PET/CT study should be rescheduled if BGL is higher than or equal to 200 mg/dL. The EANM guidelines recommend a lower acceptable upper pre-scan BGL for research purposes (i.e. between 126 and 150 mg/dL). Both guidelines suggest that pre-scan BGL may be reduced by administration of rapid acting insulin. However, the EANM guidelines also consider the impact of longer-acting insulin, and recommend specific time intervals for acceptable administration of the different types of insulin prior to scan (12). The inconsistency between different guidelines, which originates from lack of robust and credible evidence, has resulted in a diverse range of accepted prescan BGLs in clinical PET imaging. In a Web-based survey of PET/CT users, specialists from 128 PET centres in the Americas, Europe, Asia Pacific, and Middle East responded to the question regarding the pre-scan BGL cut-off used at their institutes (13). Cut-off values varied from 150 to 250 mg/dL (8.3–13.9 mmol/L), and 7% of the sites used no cut-off. Based on the recent results published in a systematic review and meta-analysis by Eskian et al (10), patients who are still hyperglycaemic after at least 4 hrs of fasting would have significantly lower FDG uptake in the brain and muscles and significantly higher FDG uptake in liver and mediastinal blood pool in comparison with euglycaemic patients. However, pooled findings reported that BGL does not have any apparent significant effect on FDG uptake of tumours. Therefore, it seems that FDG uptake ratio of tumour-to-background of normal tissues in which it is located would not decrease with hyperglycaemia. Considering the lack of significant correlation between BGL and FDG uptake in tumours, Eskian et al. recommend no interventions for hyperglycaemic patients who are scheduled to undergo PET scan, except in two conditions: BGL > 200 mg/dL or the liver as area of interest (10). In this latter condition, FDG uptake significantly increases in liver during hyperglycaemia, therefore patients should be kept euglycaemic (BGL ≤ 110 mg/dL) when liver assessment is required, in order to prevent decreased tumour-to- background uptake ratios.

There are several issues about the management of patients with diabetes and who are scheduled to undergo PET/CT scan for oncological requests.

### 1) What is the acceptable BGL for FDG PET/CT scan?

The current recommendation for brain FDG PET/CT is to limit <sup>18</sup>F-FDG administration in patients with plasma BGLs <160 mg/dL (14). It has been demonstrated that brain imaging in healthy volunteers with hyperglycaemia could reveal patterns that are similar to the findings for neurodegenerative diseases (15); therefore, the clinical indication should be kept in mind for BGL. In case of total body FDG PET/CT examination, the BGL should be lower than 200 mg/dL; if higher, the FDG PET/CT study should be rescheduled; otherwise, specific interventions should be implemented (see later).

### 2) What is the correct preparation before a FDG PET/CT scan in patients with diabetes treated with non-insulin antidiabetic agents?

Adequate pre-hydration is important to ensure a sufficiently low concentration of FDG in the urine (fewer artefacts) and for radiation safety reasons. The consumption of 1 L of water in the 2 hrs prior to FDG administration is suggested, regardless of the presence of diabetes. In patients with type 2 diabetes treated with oral antidiabetic agents, FDG PET/CT should preferably be performed late in the morning. Moreover, in order to reduce the cross reaction with the intravenous contrast agent and the physiological uptake of FDG in the intestinal loop, metformin should be discontinued at least 48 hrs before the procedure (16). No evidence is available about sulphonilureas, glinides, alpha-glucosidase inhibitors, DPP-4 inhibitors, SGLT2-inhibitors, and GLP-1 receptor agonists, whereas preliminary evidence suggests that pioglitazone has the potential to increase <sup>18</sup>F-FDG uptake of malignant lesions.

**3) What is the correct preparation before a FDG PET/CT scan in patients with diabetes treated with insulin?**

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

- a. Early in the morning, particular attention should be given to the type of insulin. In case of a long-acting insulin administered the evening before the exam, there could be a slight interference with the PET/CT study. Thus, if this is the preferred schedule, intermediate-acting insulin (effective for 12–18 h), instead of a longer acting insulin, should be recommended. Therefore, the patient should eat a normal breakfast after the PET/CT study and inject the normal amount of insulin.
- b. Late in the morning or at midday, the patient should be suggested to eat a normal breakfast early in the morning (around 7.00 a.m.) and to inject the normal amount of insulin. FDG should be injected at least 4 hrs after the subcutaneous injection of rapid-acting insulin or 6 hrs after the subcutaneous injection of regular short-acting insulin. FDG should not be administered on the same day of an injection of intermediate-acting and/or long-acting insulin.

**4) How to manage patients treated with continuous insulin infusion (i.v. or insulin pump)?**

In patients treated with continuous insulin infusion, FDG PET/CT scan should be scheduled early in the morning.

Patients on i.v. insulin infusion while in hospital are best managed by delaying the FDG scan until such intravenous therapy is no longer required, if their examination can be postponed. If urgent, i.v. insulin infusion should be stopped at least 90-120 minutes before the scan, provided that appropriate glucose target is achieved (17-18). A consultation with the local diabetes specialty team is advisable for individual advice.

People with type 1 diabetes on continuous sub-cutaneous insulin infusion can undertake the scan with the pump running on basal insulin rate alone to maintain euglycemia. Since discontinuation of the basal infusion may cause ketoacidosis, the insulin pump should not be switched off for more than 1 hour overall, if required (19). The patient can have breakfast after the FDG PET/CT study immediately restarting the continuous insulin infusion, if switched off.

**5) What is the correct preparation before a FDG PET/CT scan in patients with diabetes on artificial nutrition?**

Parenteral nutrition and intravenous fluids containing glucose should be discontinued at least 4 hrs before FDG administration. In addition, the infusion used to administer intravenous pre-hydration must not contain glucose.

**6) How to manage a patient with diabetes and with a BGL > 200 mg/dL?**

Reduction of BGLs by administration of rapid-acting insulin can be considered, but the FDG PET/CT study could also be postponed depending on the type and route of insulin administration. Unnecessary interventions aimed at lowering BGLs are sometimes time- and resources-consuming, including insulin injection, also with a potential decrease of PET scan sensitivity due to a greater muscle uptake of FDG (1). 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 BGLs periodically until an acceptable level has been achieved;
- 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 tumour-induced hyperglycaemia?**

Hyperglycaemia in these conditions should be managed as previously reported, rescheduling the scan or administering rapid-acting insulin. The withdrawal of treatments (eg, corticosteroids and chemotherapy) should be avoided and a discussion with the oncologist and diabetologist is strongly recommended.

## **APPENDIX**

AMD-AIOM 'Diabetes and Cancer' working group: Silvia Acquati, Gennaro Clemente, Romano Danesi, Stella D'Oronzo, Laura Evangelista, Daniele Farci, Pietro Ferrari, Marco Gallo, Marisa Giorgini, Valerio Napoli, Gabriella Piscitelli, Antonio Russo, Matteo Salgarello.

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