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# Positron Emission Tomography with [$^{18}$F]-FDG and Diabetes Mellitus – Practical Guidance

## *Tomografia por Emissão de Positrões com [$^{18}$F]-FDG e Diabetes Mellitus – Protocolo de Abordagem*

**Diana Borges Duarte[1], Liliana Violante[2], Isabel Torres[3], Hugo Duarte[2]**

[1]Serviço de Endocrinologia, Diabetes e Metabolismo – Centro Hospitalar e Universitário do Porto, Porto, Portugal
[2]Serviço de Medicina Nuclear – Instituto Português de Oncologia Francisco Gentil, Porto, Portugal
[3]Serviço de Endocrinologia - Instituto Português de Oncologia Francisco Gentil, Porto, Portugal

**Address**

Diana Borges Duarte
Centro Hospitalar e Universitário do Porto
Serviço de Endocrinologia
Largo Prof. Abel Salazar,
4099-001 Porto, Portugal
e-mail: diana.sbduarte@gmail.com

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**Abstract**

Current recommendations for [$^{18}$F]FDG-PET scan patient preparation have been published by various societies. The following discussion is not an in-depth review of the current guidelines nor meant to replace them, but rather to provide additional background and suggestions on how to manage patient preparation based on their diabetes therapy.

**Keywords**

Diabetes mellitus; [$^{18}$F]FDG-PET; Insulin; Diabetes therapy.

**Resumo**

As recomendações atuais para a preparação das pessoas com diabetes submetidas a PET-[$^{18}$F] FDG foram publicadas por várias sociedades científicas. A revisão elaborada não tem como objetivo substituí-las, mas sim fornecer informações adicionais e sugerir um protocolo de preparação e abordagem do paciente adequado à terapêutica hipoglicemiante em curso.

**Palavras-chave**

Diabetes mellitus; PET-[$^{18}$F]FDG; Insulina; Terapêutica hipoglicemiante.

## Introduction

Positron emission tomography (PET) is commonly used in the staging and therapeutic monitoring of various neoplasms.[1] The chemical structure of 18F-fluoro-2-deoxy-2-D-glucose ([$^{18}$F]FDG) is similar to that of glucose, differing in the marking of a carbon atom with a radioisotope of [$^{18}$F].[2] Glucose is transported by specific membrane glucose transporters (GLUT) to the cytoplasm, where it is phosphorylated by hexokinase to glucose-6-phosphate and subsequently metabolized. FDG enters cells through the same mechanism and is phosphorylated by hexokinase, but it is not a substrate for further enzymatic action with consequent intracellular accumulation.[3]

The use of FDG is based on the phenomenon of aerobic glycolysis called the "Warburg effect".[4] The increase in the rate of glycolysis of neoplastic cells is associated with the proliferative index, neovascularization, increased expression of GLUT and glucokinase with a consequent increase in uptake and concentration of [$^{18}$F]FDG.[3]

The biodistribution of [$^{18}$F]FDG in humans reflects the expression of GLUTs; in the euglycemic state, several organs and systems present a physiological uptake of [$^{18}$F]FDG, namely the brain, liver, myocardium and the urinary system.[5]

Numerous clinical conditions can affect the uptake of [$^{18}$F] FDG by tissues, hyperglycemia being the most important, either by direct competition of glucose with [$^{18}$F]FDG, or by the consequent hyperinsulinemia with overexpression of GLUT-4 and greater physiological uptake by skeletal and cardiac muscle preventing its accumulation in neoplastic cells (with risk of false negatives).[6] Plasma glucose levels may also affect the Standard Uptake Value (SUV) of tumor and/or organ lesions used as a reference such as the liver.[7]

Current recommendations for correct preparation of persons with diabetes before PET-[18F]FDG have been developed in the past.[8,9] However, the growing number of hypoglycemic therapies and new insulin formulations have increased the complexity in preparing these patients. After a review of the literature, guidelines and published consensuses,[6,8–14] a protocol proposal was developed to optimize the approach and preparation of patients with diabetes.

## I. General Considerations

1. The exam must be scheduled for early morning.
2. From midnight onwards on the day of the exam, the patient must fast (except water) and take only non-hypoglycemic medication.
3. In the 24 hours prior to the examination, food, sugary drinks or alcoholic beverages should not be ingested; physical exercise or work that requires intense muscle strength should not be performed.
4. Patients should be recommended to "simulate" during the week prior to the PET/FDG study the fasting and therapeutic changes required for the exam. If, while fasting, capillary blood glucose is >200mg/dL, they should contact their physicians for therapeutical adjustment.
5. After completing the examination, the patient should take a meal.

## II. Exam Preparation

### A. Recommendations for patients on exclusive oral hypoglycemic therapy (Table 1)

### B. Recommendations for patients undergoing insulin therapy (Tables 2 and 3)

### C. Recommendations for patients with type 1 diabetes

*Fundamental notions*

Patients with type 1 diabetes (complete absence of endogenous insulin secretion) are usually treated with a basal-bolus insulin therapy regimen. This scheme aims to mimic the physiological mechanism of pancreatic insulin secretion, consisting of:

- Basal secretion (while fasting): insulin is secreted in pulsatile and circadian cycles; the amount of insulin released is variable and relates to body mass index (and insulin resistance) and to fasting glucose.
- Stimulated secretion (postprandial/glucose load)
  - o Early/acute phase (short duration): the amount of insulin secreted depends on the magnitude of the rise in blood glucose.
  - o Late (prolonged) phase: secretion in response to absorbed "glucose load".[16]

In practice, therapy involves:

1. Multiple daily administrations

Subcutaneous administration of 2 types of insulin:

- *Basal insulin*: slow-acting insulin (Table 3)
  - o Administered 1-2 times a day (fixed dose)
- *Prandial and correction insulin*: ultra-rapid or rapid-acting insulin (Table 3)
  - o Administered before each meal (prandial bolus) – based on the carbohydrates consumed and the insulin:carbohydrates$^{\Delta}$ ratio, calculated by the assistant endocrinologist.
  - o Administered for correction of hyperglycemia (correction bolus) – using a sensitivity factor* calculated by the assistant endocrinologist.

**Table 1 –** Recommendations for patients on exclusive oral hypoglycemic therapy proposed for [$^{18}$F]-FDG PET

| Drug | Evidence | Recommended action |
|---|---|---|
| Nateglinide<br>Glipizide<br>Gliclazide immediate release | Secretagogue (Duration of action < 24h) | Suspend on the day before nor on the day of the exam (Resume medication on the following day) |
| Prolonged or modified release Gliclazide<br>Glibenclamide<br>Glimepiride | Secretagogue ( Duration of action >24h) | Suspend 48 hours before and on the day of the exam (Resume medication on the following day) |
| Metformin | May interfere with enteric glucose absorption | Suspend 48 hours before and on the day of the exam if:<br>•gastrointestinal tumor/ metastasis<br>• increased intestinal uptake of [$^{18}$F]FDG in previous examination<br>Resume medication on the following day |
| Pioglitazone | Preliminary evidence suggests that it may increase $^{18}$F-FDG uptake in tumor lesions [16] | Maintain usual therapy |
| Acarbose<br>Linagliptin<br>Sitagliptin<br>Vildagliptin<br>Saxagliptin<br>Alogliptin<br>Empaglifozin<br>Dapaglifozin<br>Ertuglifozin<br>Liraglutide<br>Dulaglutide<br>Semaglutide | No evidence against maintaining the therapy | Maintain usual therapy |

**Table 2 –** Recommendations for patients undergoing insulin therapy proposed for [$^{18}$F]-FDG PET

| Insulin | Usual administration hours | Recommended action |
|---|---|---|
| Slow acting insulin | Night | Administer as usual |
| Intermediate acting insulin<br>Premixed Insulin | Morning/afternoon | Administer only after exam |
| Ultra-rapid insulin<br>Rapid-acting insulin<br>Regular insulin | Administer as usual on the eve of the exam<br>On the day of the exam:<br>• Do not administer the insulin scheduled for breakfast ( patient is fasting)<br>• If the exam is scheduled in the afternoon, the patient can have breakfast and insulin (provided that an interval greater than 3-6h* between insulin administration and [$^{18}$F]-FDG is observed) | |

* According to duration of insulin action (see Table 3)

2. Continuous glucose infusion system ("insulin pump")

This system uses only rapid-acting or ultra-rapid-acting insulin (Table 3) and administers subcutaneous insulin through a (non-metallic) catheter placed most frequently in the abdominal, lumbar, or gluteal region.

- *Basal insulin*: the system automatically administers, every hour, a variable flow of insulin, calculated by the

**$\Delta$Insuline:carbohydrates ratio**: quantity of carbohydrates (grams) metabolized by one unit of rapid/ultra- rapid acting insulin. ***Sensitivity factor**: blood glucose value that is decreased by each unit of insulin administered (ex: 1:50→1u of rapid/ultra-rapid acting insulin decreases capillary blood glucose by 50mg/dL)

**Table 3** – Types of insulins available

| Drugs (common trade name) | Action duration |
|---|---|
| **Long-acting insulin** | |
| Degludec (*Tresiba*) | up to 42h |
| Glargina (*Lantus, Abasaglar, Semglee, Toujeo*) | 24h |
| Detemir (*Levemir*) | up to~20h$ |
| **Intermediate-acting insulin** | |
| Human isophanic insulin *(Humulin NPH, Insulatard,Insuman Basal)* | 12-18h |
| **Regular insulin** | |
| *Actrapid, Humulin, Insuman Rapid* | 6h |
| **Rapid-acting insulin (analogs)** | |
| Lispro (*Humalog*) | ~4h |
| Glulisina (*Apidra*) | ~4h |
| Aspártica (*NovoRapid*) | ~4h |
| **Ultra-rapid acting insulin** | |
| *Fiasp* | ~3h |
| *Lyumjev* | ~3h |
| **Pre-mixed insulin (rapid-acting or human + NPH)$** | |
| *Humalog Mix50* | 12-18h |
| *NovoMix30* | |
| *Humulin M3* | |
| *Mixtard 30* | |
| *Insuman Comb25* | |
| *Humalog Mix25* | |

# Duration is dose-dependent (often administered bidaily)
$ The digit in the trade name corresponds to the percentage of rapid-acting or human insulin in the premix; the duration is determined by the NPH-insulin component.

Endocrinologist. The user can reduce or increase this flow for a customized period of time (temporary basal).
- *Prandial and correction insulin*: administered by the user after providing the system with data on ingested carbohydrates and blood glucose. The system calculates the dose of insulin to be administered using these inputs and the sensitivity factor and insulin:carbohydrates ratio, programmed into the pump by the endocrinologist.

Important note: Contrarily to multiple daily administration schemes, when the continuous glucose infusion system is suspended, the patient is left without basal insulin and predisposed to events of diabetic ketoacidosis.

*Pre-examination procedure*
- Patient on multiple daily insulin administrations: follow recommendations for patients on insulin therapy (Table 2)
- Patient with insulin pump:
  - Keep in basal mode until the time of the exam; the patient must suspend and disconnect the pump before entering the PET room.
  - If prior examination shows alteration of the usual radiopharmaceutical biodistribution: ask the patient to establish a temporary basal at 50% starting 2 hours before the administration of the radiopharmaceutical.
  - The pump must not be suspended for more than one hour in total.

**D. Recommendations for exceptional situations**
- Patients undergoing continuous intravenous insulin infusion: preferably, the examination should be postponed; if urgent, intravenous infusion should be discontinued 90-120 min before administration of the radiopharmaceutical. Contact Endocrinology.
- Patients on intravenous fluid therapy with glucose or on parenteral nutrition: should be discontinued at least 4 hours before radiopharmaceutical administration.

## III. Hyperglycemia approach (capillary blood glucose >200mg/dL)

In the Nuclear Medicine Service, insulin pens used to correct hyperglycemia (lispro, glulisine or aspartic) must be kept in the refrigerator until the first use. After the first use, they must be stored at room temperature, in a dry place and without significant fluctuations in temperature (the administration of cold insulin delays absorption and, consequently, its hypoglycemic effect). Once used, the insulin pen is valid for 30 days.

If capillary blood glucose >200mg/dL documented on admission to the Nuclear Medicine service, the following procedures can be adopted:
- Postponement of the exam, with indication to contact the treating physician for adjustment of antidiabetic medication.
- Hydration with blood glucose reassessment every 30 minutes: recommended for blood glucose levels slightly above target (200-225mg/dL).

- Correction with subcutaneous ultra-rapid/rapid acting insulin.

If the last alternative is chosen, the correction should be guided by algorithms 1 and 2. In patients with an insulin pump, the patient should be asked to perform a correction bolus, using the pre-defined parameters of the infusion system.

Capillary blood glucose should be assessed and recorded every 30 minutes. Administration of the radiopharmaceutical must wait at least 3 hours (in the case of ultra-rapid-acting insulins) or 4 hours (in the case of rapid-acting insulins) after the time of subcutaneous injection of insulin.

**Algorithm 1 – Hyperglycemia correction scheme for patients under exclusive oral hypoglycemic therapy and without obesity**

| Doentes sob terapêutica hipoglicemiante oral exclusiva e IMC≤30kg/m² | | | |
|---|---|---|---|
| **Glucose range (mg/dL)** | **Units (U) of rapid-acting or ultra-rapid-acting insulin to be administered** | **Waiting time until administration of [18F]FDG (hours)** | |
| | | **Ultra-rapid acting insulin** | **Rapid-acting insulin** |
| 200-250 | 3 U | 3 | 4 |
| 251-300 | 4 U | | |
| 301-350 | 5 U | | |
| 351-400 | 6 U | | |
| 401-450 | 7 U | | |
| 451-500 | 8 U | 3-5* | 4-6* |
| >500 | 10 U | 3-5* | 4-6* |

*With larger insulin doses, the estimated duration of active insulin is higher: assess capillary blood glucose every 15min after 3h or 4h (if ultra-rapid or rapid-acting insulin, respectively), if 3 measurements with variation < 30mg/dL are made, it can be assumed that the insulin in circulation is negligible, and the radiopharmaceutical may be administrated.

**Algorithm 2** – Hyperglycemia correction scheme for obese patients under insulin therapy or corticoid therapy

| Patients on insulin therapy** or patients with BMI ≥30kg/m² or patients under supraphysiological corticosteroid therapy *** | | | |
|---|---|---|---|
| **Glucose range (mg/dL)** | **Units (U) of rapid-acting or ultra-rapid-acting insulin to be administered** | **Waiting time until administration of [$^{18}$F]FDG (hours)** | |
| | | **Ultra-rapid acting insulin** | **Rapid-acting insulin** |
| 200-240 | 4 U | 3 | 4 |
| 241-280 | 6 U | | |
| 281-320 | 7 U | | |
| 321-360 | 8 U | 3-5* | 4-6* |
| 361-400 | 9 U | | |
| 401-440 | 10 U | | |
| 441-480 | 11 U | | |
| 481-520 | 12 U | | |
| >520 | 13 U | | |

*With larger insulin doses, the estimated duration of active insulin is higher: assess capillary blood glucose every 15min after 3h or 4h (if ultra-rapid or rapid-acting insulin, respectively), if 3 measurements with variation < 30mg/dL are made, it can be assumed that the insulin in circulation is negligible, and the radiopharmaceutical may be administrated.

** In patients taking rapid insulin in an outpatient setting, the patient's own correction scheme can be requested and administered.

*** Greater than 5mg of prednisolone/day or equivalent

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*Protection of human and animal subjects*: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).
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