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The Effect of Glucose on Quality of PET Scan Results

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Abstract

Positron Emission Tomography (PET) imaging is a metabolic imaging technique using a radioactive tracer, ^{18}F-fluorodeoxyglucose (^{18}F-FDG), to identify the presence and severity of disease, namely cancers. Most malignant tissues have increased ^{18}F-FDG uptake associated with an increased rate of glycolysis and of glucose transport. The increase in ^{18}F-FDG uptake noted in malignant tissues is related in a complex manner to the proliferative activity of malignant tissue and information regarding the location of abnormal levels of radioactive glucose obtained from a PET scan helps clinicians effectively pinpoint sources of cancer and progression of disease. According to the 2011 census, a total of 1,853,700 clinical PET and PET/CT studies were performed at over 2,200 U.S. locations[1]. Appropriate patient preparation plays an important role in obtaining good quality images, which is essential for accurate interpretation as the concentration of circulating glucose can significantly affect ^{18}F-FDG uptake by tumors. Relevant considerations before the study include restrictions of diet and activity, management blood glucose levels in patients with diabetes, as well as an awareness of the effect of medications and environmental conditions. Important protocol guidelines for performing PET and PET/CT have been proposed by various societies and groups, including the Society of Nuclear Medicine and Molecular Imaging (SNMMI), the European Association of Nuclear Medicine (EANM), the American College of Radiology (ACR), the National Cancer Institute (NCI), and the Netherlands society of nuclear medicine.

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Introduction

Dietary Restriction

Per the SNMMI, patients should be instructed to fast and not consume liquids except for water for at least 4 - 6 hours before radiotracer injection. Parenteral nutrition or intravenous (IV) fluids containing dextrose should also be withheld for 4 - 6 hours[2]. The EANM suggests patients not consume any food or sugar for at least 6 hours before injection of ^{18}F-FDG and that parenteral nutrition and IV fluids containing glucose should be discontinued at least 4 hours before the PET scan[3]. The NCI consensus and the ACR similarly recommend that patients should fast with no oral or IV fluids containing glucose for a minimum of 4 hours before the PET scan[4,5]. A review of the available literature regarding patient preparation prior to a PET scan recommends minimizing dietary glucose-related competitive inhibition of ^{18}F-FDG and reducing serum insulin to near basal levels including cessation of enteral nutrition, dextrose-containing intravenous fluids, and parenteral nutrition. Fasting should occur for a minimum of 6 hours before the scan. During this time only plain water should be permitted, and there should be absolutely no carbohydrate intake of any kind, including gum, candy, or breath mints[6]. Most guidelines recommend good hydration, typically orally prior to the study for safety of receiving radiation and to ensure a low ^{18}F-FDG concentration in the urine. The amount of hydration recommended varies from 0.5 to 2L of plain water as tolerated during fasting period[2-5].

The NCI recommends a low-carbohydrate diet for 24 hours before the PET scan[4]. A proposed standardized protocol published in 2014 by the Division of Molecular Imaging and Therapeutics at the University of Alabama at Birmingham recommends a high-protein, low-carbohydrate diet for 24 hour be-

fore scanning to minimize dietary glucose-related competitive inhibition of ^{18}F-FDG uptake. Below is the sample menu they recommend[6]. However, a specific restriction on the quantity (grams) of carbohydrates has not been recommended by any of the aforementioned societies.

Sample Menu 24 hours prior to PET scan

Sample menu:

• Main course: Beef, turkey, pork including bacon, fish, chicken, eggs.

• Vegetables: Broccoli, asparagus, cauliflower, zucchini, spinach, mushrooms.

• Desserts: Cheese, cottage cheese.

• Drinks: Unsweetened black coffee, unsweetened tea, water, Artificial sweeteners are not permitted.

• Carbohydrates/sugars to be avoided: Bread, bagels, cereal, cookies, toast, pasta, crackers, muffins, peanut butter, nuts, fruit, fruit juice, potatoes, candy, rice, cornbread, carrots, beets, chewing gum, mints, cough drops, and sweet soft drinks.

• Patients are encouraged to stay well hydrated. Recommend 2L of plain drinking water in the 4-h period immediately before PET/CT. Continued hydration as tolerated is recommended after scan completion to enhance ^{18}F-FDG excretion.

Activity Restriction

The EANM recommends that patients abstain from extreme exercise for at least 6 hours before the PET scan, and both the NCI and ACR recommend avoiding strenuous activity for 24 hours before[3-5]. The 2014 standardized protocol recommends that exercises such as jogging, cycling, weightlifting, strenuous housework and yard work be avoided for a minimum of 24 hours[6]. Patients should also not chew gum for 24 hours before the PET scan as this has been shown to activate masticatory muscles[7].

Medications

The EANM specifies no restrictions and that all medications should be taken as prescribed[3]. Medication restrictions or considerations are not discussed in the other aforementioned guidelines. However, the medication profile of each patient should be reviewed and taken into consideration as several commonly prescribed medications can elevate serum glucose levels, for example, glucocorticoids, phenothiazines, lithium, tricyclic antidepressants, phenytoin, and thiazide diuretics[7,8]. With glucocorticoids, the PET scan may need to be coordinated either before or after their use[9,10]. Agents such as nicotine and sympathomimetics are known to activate brown adipose tissue and in turn increase ^{18}F-FDG uptake, which can potentially mask or mimic malignant tissue. As such, these agents should be held before the PET scan[15].

Patients with diabetes

Blood glucose levels can have a significant influence on ^{18}F-FDG uptake in tumors because ^{18}F-FDG and glucose compete for glucose transport and phosphorylation for use by the cell. There is a well-known association between plasma glucose levels, serum insulin levels, and their effect on the bio-distribution of ^{18}F-FDG. Cancer cells take up relatively more ^{18}F-FDG than glucose when the extracellular glucose concentration is low, resulting in higher standard uptake values (SUV) after fasting[14]. Increased glucose levels decrease ^{18}F-FDG uptake in the brain and in tumors because of indirect competition between binding sites and enzymes[11,12]. Increased insulin secretion secondary to elevated blood glucose increases the translocation of GLUT4 (glucose transporter), thereby rapidly and efficiently shunting ^{18}F-FDG to organs with a high density of insulin receptors, like cardiac and skeletal muscles, resulting in altered radiotracer bio-distribution and suboptimal image quality[13]. A study by Lindholm et al., showed that SUVs decrease significantly in all tumors studied after a 50g loading dose of glucose ($p < 0.02$). In this study, muscle tissues accumulated more ^{18}F-FDG than did the tumor tissues after the administration of 50g dose of glucose when compared to a fasting state[14]. A study by Boellaard et al., also reported lower uptake levels with increasing blood glucose levels. The SNMMI recommends a pre-scanning glucose level between 150 and 200 mg/dL and suggests that reducing the serum glucose level by administering insulin can be considered but that the administration of ^{18}F-FDG should be delayed after insulin administration. The duration of the delay should be determined by the type and route of administration of insulin[2].

The EANM suggests that PET scan can be performed if the blood glucose is < 120 mg/dL and that if insulin is given to reduce the blood glucose levels, the interval between administration of insulin and ^{18}F-FDG should be more than 4 hours[3]. The NCI consensus recommends that the pre-scanning blood glucose be < 120 mg/dL in patients without diabetes, and between 150 and 200 mg/dL in patients with diabetes. The NCI recommends against the use of insulin to reduce blood glucose levels and that the study should be rescheduled if serum glucose > 200 mg/dL[3].

Despite the above recommendation against the use of insulin to correct hyperglycemia, several publications have cited successful use of intravenous regular insulin to correct hyperglycemia that occurs immediately before an ^{18}F-FDG PET scan. In one study, when ^{18}F-FDG was injected 1 hour after a bolus administration of intravenous insulin in hyperglycemic patient with diabetes according to a pre-established chart to reach a target serum glucose < 144 mg/dL, no difference was seen in SUV between normoglycemic patients without diabetes and the insulin corrected hyperglycemic patients with diabetes[15]. A more recent study conducted by Caobelli et al., proposed an optimized protocol for intravenous insulin administration in patients with diabetes undergoing ^{18}F-FDG PET imaging. They used short-acting intravenous regular insulin and ^{18}F-FDG was injected 30 min after insulin administration. No significant difference was seen between the hyperglycemic patients and the normoglycemic patients[16]. Roy et al., used a standardized insulin administration protocol of short-acting intravenous regular insulin to reach a target serum glucose < 180 mg/dL at least 1 hour before ^{18}F-FDG administration. The protocol was shown to be safe and effective in decreasing glucose levels, but led to an altered bio-distribution (increased muscle uptake and decreased liver intake) in 25% of patients. It was discovered that the interval between insulin injection and ^{18}F-FDG injection was significantly shorter in patients with altered bio-distribution and as such they recommend an interval of at least 90 minutes[17]. A case report describing qualitatively normal ^{18}F-FDG bio-distribution after subcutaneous administration of long-acting insulin glargine 3 hours before ^{18}F-FDG injection was attributed to the time-activity profile, which mimics the normal basal secretion of insulin by the pancreas[18].

The 2014 standardized protocol recommends that patients with diabetes check their blood glucose level at home on days leading up to their PET scan to ensure reasonable blood glucose levels (< 200 mg/dL) and for individuals with blood glucose levels > 200 mg/dL, the PET scan should be rescheduled. For patients on long acting insulin, they recommend early testing after an overnight fast. For patients on short-acting insulin, they recommend testing ~6 hours post insulin administration and a low-carbohydrate meal. Administration of intravenous regular insulin would require extensive training of staff, frequent blood glucose monitoring, and identification and correction of potential hypoglycemia. At this time, this practice is not recommended[6].

Prominent bowel uptake of ^{18}F-FDG has been identified with use of metformin and this can compromise the quality of the image. Gontier et al., conducted a prospective study to determine the impact of anti-diabetic medications on ^{18}F-FDG bowel uptake in patients with type 2 diabetes. The study showed that ^{18}F-FDG bowel uptake was significantly higher in patients treated with metformin when compared to patients without diabetes ($p < 0.0001$). Several studies have demonstrated that withholding metformin prior to a PET scan resulted in significantly less uptake of ^{18}F-FDG. As such, it is reasonable to hold metformin for 48 hours prior to the PET scan[19-22].

Pre-Medication Considerations

Benzodiazepines have been successfully used before PET imaging to relieve anxiety in patients and to relax skeletal muscles. Some theorize this reduces the amount of ^{18}F-FDG uptake in brown adipose tissue as well, but this is questionable. A randomized controlled trial evaluating the effects of oral diazepam on the neck and upper chest muscles and on brown adipose tissue uptake of ^{18}F-FDG found no significant difference[23-25]. The previously mentioned societies recommend that the administration of sedatives is at the discretion of the clinician for use in extremely anxious patients or if the area of interest is the head and neck[2-5].

Conclusion

PET imaging using ^{18}F-FDG as a radioactive tracer is a frequently used study in the evaluation of patients with cancer. Circulating serum glucose has been implicated in affecting the quality of images obtained from the study. Circulating serum glucose levels are affected by comorbid conditions, diet, exercise, and medications however, it remains unclear the amount of circulating glucose necessary to interfere with the studies and what should be done to mitigate this problem. It does appear that patient preparation plays an important role in obtaining good quality images although there is currently no consensus on how to best prepare patients for PET imaging. An attempt was made in 2014 by Surasi, et al., to develop a standardized protocol for patient preparation in PET imaging, however this has not been adopted by any of the aforementioned societies. Current practice is dictated by local protocols provided by the facilities that offer PET imaging.

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