^{18}F-FDG PET and PET/CT Patient Preparation: A Review of the Literature*

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For many types of cancer, ^{18}F-FDG PET/CT is commonly used in evaluation and management, including tumor diagnosis, staging, restaging, treatment monitoring, and radiation therapy planning. Meticulous patient preparation including restrictions of diet and activity and management of blood glucose levels in diabetic patients, as well as an awareness of the effect of medications and environmental conditions, plays an important role toward obtaining good-quality images, which are essential for accurate interpretation. Protocol guidelines for performing PET/CT have been proposed by various societies and groups, including the Society of Nuclear Medicine and Molecular Imaging, the European Association of Nuclear Medicine, the American College of Radiology, and the National Cancer Institute. Standardization of the PET/CT procedure is necessary to enable use of metabolic parameters as imaging biomarkers in routine clinical decision making and to ensure reproducibility and allow comparison examinations across different sites. Though several published articles, including various society guidelines, have addressed the relevant patient preparation variables individually, we believe there is need for further clarification. This article summarizes existing data and proposes a standard patient preparation protocol.

Key Words: ^{18}F-FDG PET/CT; patient preparation; standardization; consensus guidelines; oncology

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In clinical practice, ^{18}F-FDG PET/CT is commonly used in the evaluation and management of many types of cancer, including tumor diagnosis, staging, restaging, treatment monitoring, and radiation therapy planning. Oncologic imaging with PET has recently gained particular importance in the quest to identify new and effective therapies and to understand the role of molecular biomarkers in treating cancer.

According to the 2012 PET Imaging Market Summary Report published by International Marketing Ventures, PET and PET/CT studies were performed at over 2,200 U.S. locations using fixed or mobile scanners and, per a 2011 census, a total of 1,853,700 clinical PET/CT and PET studies were performed in the United States, with oncology, cardiology, neurology, and others constituting 94% (1,736,800), 3% (53,300), 3% (58,000), and less than 1% (5,600), respectively (*1*).

Meticulous patient preparation plays an important role toward obtaining good-quality images, which are essential for accurate interpretation of the PET/CT studies. Relevant considerations before the study include restrictions of diet and activity and management of blood glucose levels in diabetic patients, 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 (*2–6*). Quantification of ^{18}F-FDG uptake is a useful tool in addition to qualitative interpretation of images, as the percentage change in tumor standardized uptake value (SUV) is more reproducible than the percentage change in CT tumor size (*7*). However, SUV is affected by several variables, including those related to patient preparation, blood glucose, uptake period, scan acquisition, image reconstruction, and region-of-interest parameters (*8,9*).

The published literature has reported considerable variability in the way PET/CT scans are obtained. This variability likely makes it difficult to quantitatively compare studies performed at different centers. An Imaging Response Assessment Team funded by the NCI developed and conducted a 34-question survey among 15 institutions about how clinical PET/CT studies were performed and found considerable variability (*10*). Protocol variability was also reported by another international study based on a World Wide Web survey of public and private imaging centers performed to assess current PET/CT protocols (*11*).

Therefore, standardization of the PET/CT procedure is necessary to enable use of metabolic parameters as imaging biomarkers in routine clinical decision making, ensure reproducibility, and allow comparison examinations across

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different sites. Though several published articles, including various society guidelines, have addressed the relevant patient preparation variables individually, we believe there is need for further clarification. This article summarizes existing data and proposes a standard patient preparation protocol for oncologic ^{18}F-FDG studies that can be easily incorporated into daily clinical practice. The proposed protocol is described in Table 1, and a comparison of our proposed protocol with the recommendations of the SNMMI, EANM, ACR, and NCI is presented in Table 2. Readers are directed to previous publications (*12–16*) for detailed information on oral and intravenous contrast agents, CT protocols for diagnostic whole-body ^{18}F-FDG PET/CT, and dedicated brain and cardiac ^{18}F-FDG PET imaging, which are beyond the scope of this review.

DIETARY INSTRUCTIONS

Fasting

To minimize dietary glucose–related competitive inhibition of ^{18}F-FDG uptake and reduce serum insulin to near basal levels, we recommend complete fasting for a minimum of 6 h before the scan, including cessation of tube feeding, dextrose-containing intravenous fluids, and parenteral hyperalimentation. During this time, only plain (unflavored) water is permitted, and there should be absolutely no sugar or carbohydrate intake of any kind, including gum, candy, or breath mints. Similar recommendations with subtle differences are found in the various society guidelines. Per the SNMMI, patients should be instructed to fast and not consume liquids except for water for at least 4–6 h before radiotracer injection. Intravenous fluids containing dextrose or parenteral feedings should also be withheld for 4–6 h (*2*). The EANM suggests that patients not consume any food or sugar for at least 6 h before injection of ^{18}F-FDG. Thus, patients scheduled to undergo the PET study in the morning should not eat after midnight and preferably should have a light meal without alcohol on the evening before the PET study. Those scheduled for an afternoon examination may have a light breakfast before 8:00 AM (i.e., up to 2 sandwiches without sugars or sugar-containing sandwich fillings). Parenteral nutrition and intravenous fluids containing glucose should be discontinued at least 4 h before the PET/CT examination (*3*). The NCI consensus recommendations proposed that patients should fast for a minimum of 4 h before ^{18}F-FDG injection and that if the study is scheduled for the afternoon, a light breakfast with minimal carbohydrate-containing foods is acceptable (*4*). The ACR recommends a minimum of 4 h of fasting, with no oral or intravenous fluids containing sugar or dextrose (*5*). Per the survey of the Imaging Response Assessment Team (*10*), the most reasonable recommendation was fasting for at least 4 h and preferably 6 h. According to the international Web survey (*11*), the average fasting period before oncologic ^{18}F-FDG PET/CT varied among users: 0–4 h (27%), 5–6 h (51%), 7–8 h (9%), or more than 8 h (13%).

Hydration

Most guidelines recommend good hydration, typically oral, before the study for radiation safety reasons and to ensure a low ^{18}F-FDG concentration in urine. The EANM recommends 1 L of water by mouth in the 2 h before injection and favors another 0.5 L during the uptake period as tolerated (*3*). The NCI recommends that patients should consume at least 2–3 12-oz (355 mL each) glasses of water during fasting and another 250–500 mL of water after injection and before scanning (*4*). Our preference is to have patients drink 1–2 L of plain water as tolerated during the 4 h immediately before the PET/CT scan. All patients are asked to void just before imaging.

Specific Diet

We recommend a high-protein, low-carbohydrate diet for 24 h before scanning to minimize dietary glucose–related competitive inhibition of ^{18}F-FDG uptake. A sample menu is described in the proposed standard patient preparation protocol (Table 1). Alcohol and nicotine products are completely avoided for 12 h before the scan. The NCI also recommends a low-carbohydrate diet for 24 h before the study (*4*). About half of the Imaging Response Assessment Team sites recommended a low-carbohydrate diet to their patients (*10*). Per the international survey (*11*), about one third of the responders reported requiring dietary restrictions such as no caffeine, a low-carbohydrate diet, or nothing taken orally.

ACTIVITY RESTRICTION

We recommend that exercises such as jogging, cycling, weightlifting, strenuous housework, yard work, and sexual activity be avoided for a minimum of 24 h (ideally 48 h) before the scan to minimize uptake of radiotracer in skeletal muscles (Fig. 1). Patients are also advised not to chew gum for 24 h before the study to avoid activation of masticatory muscles (*17*). The EANM suggests that all patients avoid (extreme) exercise for at least 6 h before the PET study (*3*). Both the NCI and the ACR recommend avoiding strenuous activity for 24 h before injection (*4,5*).

MEDICATION

All prescription medications should be taken as directed (insulin and oral hypoglycemics are discussed in greater detail in the next section). The PET center personnel need to recognize that several commonly prescribed medications can elevate serum glucose levels, including glucocorticoids, phenothiazines, lithium, tricyclic antidepressants, phenytoin, thiazide diuretics, isoniazid, rifampin, and ephedrine (*17, 18*). Notably with glucocorticoids, the PET examination may have to be coordinated either before or after their use or, alternatively, the associated hyperglycemia may need remedial therapy with insulin (*19,20*). We do not recommend that patients stop taking any of the above medications before their PET scan. The EANM specifies no restrictions and that medication can be taken as prescribed (*3*).

TABLE 1
Proposed Standard Patient Preparation Protocol for ^{18}F-FDG PET and PET/CT

Dietary Instructions
- Complete food fasting is required, including cessation of tube feedings, dextrose-containing intravenous fluids, and parenteral hyperalimentation (minimum of 6 h before scan).
- Only plain water is permitted; flavored water is not allowed (6 h before scan).
- Absolutely no sugar or carbohydrate intake of any kind is allowed, including candy or breath mints (6 h before scan).
- No caffeine, alcohol, and nicotine products are allowed (12 h before scan).
- A high-protein, low-carbohydrate diet is required (24 h before 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 2 L 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 (Minimum 24 h Before Study, Although 48 h Is Ideal)
- Exercises such as jogging, cycling, weightlifting, strenuous housework, yard work, and sexual activity should be avoided.
- Patients are advised not to chew gum.

Medications
- All prescription medications should be taken as directed (insulin and oral hypoglycemics are discussed under "Diabetic Patients").

Diabetic Patients
- Home blood glucose checks should be performed in the days leading to the PET exam to ensure adequate blood glucose levels (≤200 mg/dL).
- All prescription oral diabetes medications should be taken as directed.
- Metformin may be discontinued for 2 days before the study if there are gastrointestinal tumors (to minimize inadvertent gastrointestinal uptake) or if there has been prominent gastrointestinal uptake on prior PET studies.
- Patients on regular insulin should take their normal amount of insulin along with breakfast by 6 AM. They should be scheduled between 12 noon and 1 PM. Alternatively, those receiving evening or bed-time long-acting insulin should be scheduled at 7 AM after an overnight fast.
- Patients on continuous insulin infusion/pump are scheduled early in the morning (by 8 AM) and eat breakfast after the PET study. The insulin pump is kept on the night/basal setting until after the PET study.

Strategies for addressing hyperglycemia (>200 mg/dL) immediately before ^{18}F-FDG PET study:
- Reschedule scan, encourage frequent home blood glucose checks, and ask patient to contact primary care physician for further guidance on glycemic control (OR)
- Start regimen of intravenous short-acting regular insulin. (Implementation requires staff with extensive training on use of intravenous insulin, frequent blood sugar monitoring, and identification and correction of potential hypoglycemia.)
  2 units for blood sugar between 201 and 250 mg/dL.
  3 units for blood sugar between 251 and 300 mg/dL.
  4 units for blood sugar between 301 and 350 mg/dL.
  5 units for blood sugar between 351 and 400 mg/dL.
  Target blood sugar is ≤200 mg/dL.
  ^{18}F-FDG is injected at least 60 min (ideally 90 min) after insulin administration.

Premedication (as Needed)
- For patients with head and neck cancer, claustrophobia, anxiety, or a need to relax skeletal muscles: Oral alprazolam, 0.5 mg, at the time of ^{18}F-FDG injection. (Patients should be warned against driving because of sedating effects and psychomotor impairment.)
- For patients with prominent brown adipose tissue uptake: Oral β-blocker propranolol, 20 mg, 1 h before ^{18}F-FDG injection. (Heart rate and blood pressure monitoring must be performed while the patient is in the PET clinic.)

Environmental Conditions
- Patients should avoid cold exposure for 2 d before the study.
- Patients should avoid air conditioning on the day of the study.
- Patients should keep the car windows rolled up during travel to the PET/CT clinic and, if necessary, use a car heater on cool days.
- Patients should wear warm clothing, including long pants or slacks, long sleeves in summer (no shorts or tank tops), and a sweater, jacket, and cap on cold or even slightly cool days.
- Maintain a warm room temperature (minimum, 75°F), and provide warm blankets during the uptake period.

GLUCOSE LEVELS, INSULIN, AND ANTIDIABETIC MEDICATION

Blood glucose levels can have a significant influence on tumor ^{18}F-FDG uptake because ^{18}F-FDG and glucose compete for glucose transport and phosphorylation by hexokinase (*21*). There is a well-known association between plasma glucose levels, serum insulin levels, and their effect on the biodistribution of ^{18}F-FDG. Increased glucose levels decrease ^{18}F-FDG uptake in the brain and in tumors because of direct competition between binding sites and enzymes (*22*). Increased insulin secondary to elevated blood glucose increases the translocation of GLUT4

TABLE 2
Patient Preparation Recommendations

Category	SNMMI (*2*)	EANM (*3*)	ACR (*5*)	NCI (*4*)	Proposed standard protocol
Fasting period	At least 4–6 h	At least 6 h	Minimum of 4 h	Minimum of 4 h	Minimum of 6 h
Hydration	Oral hydration with water	1 L of water by mouth 2 h before injection; 0.5 L of water during uptake period as tolerated	Typically oral hydration, intravenous in special circumstances	At least 2–3 (12 oz [355 mL] each) glasses of water during fasting and 250–500 mL of water after injection and before scanning	1–2 L of plain water as tolerated during the 4 h immediately before PET/CT scan
Diet	Not stated	Not stated	Not stated	Low-carbohydrate diet for 24 h	High-protein, low-carbohydrate diet for 24 h
Physical activity/exercise restriction	Not stated	At least 6 h before PET study	1 d before scan	1 d before scan	Avoid for minimum of 24 h (ideally 48 h) before scan
Medications	Not stated	Take as prescribed	Not stated	Not stated	Take as directed
Glucose level before tracer injection	150–200 mg/dL	<120 mg/dL (<7 mmol/L)	Not stated	Nondiabetic patients,<120 mg/dL; diabetic patients, 150–200 mg/dL	<200 mg/dL
Premedication	Lorazepam or diazepam before ^{18}F-FDG injection to reduce uptake by BAT and skeletal muscle or β-blockers to reduce BAT uptake	Sedatives such as short-acting benzodiazepines in patients with head and neck tumors, anxiety, or claustrophobia	Premedication for anxiety, if indicated, without mention of a specific recommendation	A sedative such as diazepam in extremely anxious patients or when area of interest is head and neck	Oral alprazolam, 0.5 mg, for patients with head and neck cancer, claustrophobia, or anxiety; oral β-blocker (propranolol, 20 mg) 1 h before ^{18}F-FDG injection for patients with prominent BAT
Timing of PET	Not stated	10 d after last chemotherapy dose; 3 mo after radiation	Not stated	At least 2 wk after end of a specific chemotherapy cycle; 6–8 wk or longer after radiation therapy	At least 2 wk after end of last chemotherapy cycle; 6-8 wk after surgery; 12 wk after radiation

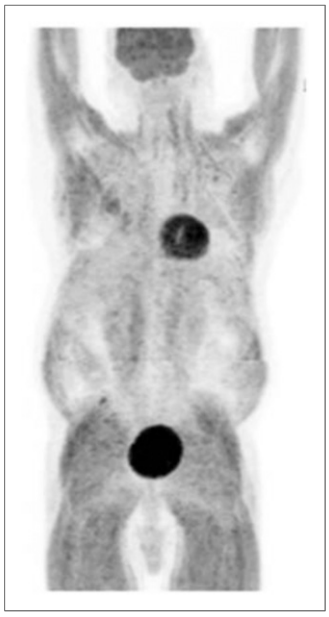

FIGURE 1. Effect of exercise on skeletal muscle ^{18}F-FDG uptake. Maximum-intensity-projection image of ^{18}F-FDG PET study demonstrates prominent diffuse ^{18}F-FDG uptake in skeletal and cardiac muscles in patient who performed strenuous exercises in the 2 d before undergoing PET.

(glucose transporter), thereby rapidly and efficiently shunting ^{18}F-FDG to organs with a high density of insulin receptors (e.g., skeletal and cardiac muscles), resulting in altered radiotracer biodistribution and suboptimal image quality (*23*).

Lindholm et al. showed that SUVs decrease significantly in all tumors studied when ^{18}F-FDG PET imaging is done after a 50-g loading dose of glucose ($P < 0.02$). In contrast to the tumors, the muscle tissue accumulated more ^{18}F-FDG after glucose loading than in the fasting state, resulting in blurring of tumor margins. Cancer cells take up relatively more ^{18}F-FDG than unlabeled glucose when the extracellular glucose concentration is low, resulting in higher SUVs in the fasting state (*24*).

Boellaard also reported lower uptake levels or SUVs with increasing blood glucose levels, with the range of SUV being between −15% and +15% (*25*).

In a busy PET clinic, there are many scenarios involving diabetic individuals that may affect patient preparation and the quality of ^{18}F-FDG PET/CT images. For example, the patient may be in a state of hyperglycemia immediately before the PET study, and interactions with diabetic medications such as metformin and insulin may occur. Considering the growing number of diabetic patients who have cancer, hyperglycemia before a PET/CT study is not uncommon. Several publications have cited successful use of intravenous regular insulin to correct hyperglycemia that occurs immediately before an ^{18}F-FDG PET/CT scan. In one study (*26*), when ^{18}F-FDG was injected 1 h after a bolus administration of intravenous insulin in hyperglycemic diabetic patients (Humulin R [Elli Lilly], according to a preestablished chart to reach a target glycemia of lower than 8 mmol/L [144 mg/dL]), no differences in SUV for lungs, liver, muscles, myocardium, or suspected pulmonary lesions were found between normoglycemic nondiabetic patients and the insulin-corrected hyperglycemic diabetic patients.

A more recent study conducted by Caobelli et al. proposed an optimized protocol for intravenous insulin administration in diabetic patients undergoing ^{18}F-FDG PET/CT (*27*). They used short-acting intravenous Humulin R (25 units; diluted in 250 mL of physiologic solution [infusion rate in mL/h determined as glucose level divided by 20]), and ^{18}F-FDG was injected 30 min after insulin administration. No significant difference in the gluteal muscle SUVs were observed between the hyperglycemic patients (>180 mg/dL) who received the insulin and the control groups, which included the hyperglycemic patients (160–200 mg/dL) who did not receive insulin and the nondiabetic patients.

In 63 diabetic cancer patients, Roy et al. used a standardized protocol of short-acting intravenous Humulin R (2 units for glycemia of 10.0–12.0 mmol/L [180–216 mg/dL], 3 units for 12.1–14.0 mmol/L [216–252 mg/dL], and 4–6 units for ≥14.1 mmol/L [≥252 mg/dL]) to reach a target glycemia lower than 10.0 mmol/L (180 mg/dL) at least 1 h before ^{18}F-FDG injection (*28*). Their protocol was safe and effective in decreasing glucose levels but led to an altered biodistribution in 25% of patients (increased muscle uptake and decreased liver uptake). The interval between insulin injection and ^{18}F-FDG injection was significantly shorter in patients with an altered biodistribution than in those with a normal biodistribution (65.7 vs. 80.2 min, $P < 0.01$). Their tentative recommendation was to maintain an interval of 90 min between insulin injection and ^{18}F-FDG injection.

Nakatani et al. studied 44 patients with extensive skeletal muscle uptake of ^{18}F-FDG after a fast of at least 4 h (*29*). They concluded that both glucose intolerance and gastric food residue are independent risk factors for increased skeletal muscle uptake and suggested a longer fasting time in patients with glucose intolerance and avoidance of a heavy meal before the study to reduce gastric residue.

The impact of elevated blood glucose levels, diabetes, insulin treatment, and obesity on ^{18}F-FDG uptake in tumors and biodistribution in normal organ tissues was studied by Busing et al. (*30*). Hyperglycemia was associated with decreased cerebral uptake and increased skeletal muscle uptake. The mean cerebral maximum SUV was significantly decreased whereas the mean muscular maximum SUV was increased by up to 31% in diabetic and insulin-treated patients compared with nondiabetic and non–insulin-treated patients ($P < 0.001$).

A case report describing qualitatively normal ^{18}F-FDG biodistribution after subcutaneous administration of long-acting insulin analog glargine (Lantus; Sanofi-Aventis) 3 h before ^{18}F-FDG injection was attributed to the time–activity profile of insulin glargine, which mimics the normal basal secretion of insulin by the pancreas (*31*).

In our clinical practice, diabetic patients are encouraged to check their blood glucose level at home on the days leading up to their PET/CT examination to ensure reasonable blood glucose levels (≤200 mg/dL). If the blood glucose levels are consistently greater than 200 mg/dL, we recommend that they contact their primary care physician for further

guidance on glycemic control. Fasting and meal instructions are given as detailed in "Dietary Instructions" above. All oral medications, including those for diabetes, such as metformin, are to be taken as prescribed. Diabetic patients on regular short-acting insulin take their insulin along with breakfast by 6 AM. These individuals are usually scheduled for imaging between 12 PM and 1 PM. Alternatively, those receiving evening or bedtime long-acting insulin can be scheduled for imaging at 7 AM after an overnight fast. Patients on a continuous insulin infusion or pump are scheduled early in the morning (by 8 AM) and asked to eat breakfast after the PET study. The insulin pump is kept on the night or basal setting until after the PET study. For individuals who present with hyperglycemia (blood glucose $>$ 200 mg/dL), we reschedule the scan and ask that they frequently check their blood glucose at home and contact their primary care physician. They are asked to contact the PET center with the results of their blood glucose checks in the days leading up to the rescheduled PET study. We are considering implementing a standardized protocol using intravenous short-acting regular insulin to correct hyperglycemia before the PET study in an effort to decrease patient inconvenience and improve resource use. Implementation of such a protocol would involve extensive training of staff on the use of intravenous insulin, frequent blood glucose monitoring, and identification and correction of potential hypoglycemia (*32*).

The SNMMI recommends a prescanning glucose level of 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 (with the duration of the delay depending on the type and route of administration of insulin) (*2*). The EANM suggests that an ^{18}F-FDG study can be performed if the blood glucose level is less than 7 mmol/L (120 mg/dL). The EANM also specifies that if insulin is to be given to reduce the blood glucose level, the interval between administration of insulin and administration of ^{18}F-FDG should be more than 4 h. For type II diabetic patients controlled by oral medication, patients can continue to take the oral medication and the PET study should preferably be done in the late morning. For insulin-dependent type II and type I diabetic patients, the PET study should preferably be scheduled for the late morning and the patient should eat a normal breakfast at 7 AM, inject the normal amount of insulin, and not consume any more food or fluids, apart from water, afterward. For patients on a continuous insulin infusion, the PET study should be scheduled early in the morning. The insulin pump is kept on the night setting until after the study, at which time the patients can also have breakfast (*3*). The NCI consensus recommended that the venous serum glucose be within 120 mg/dL for nondiabetic patients and 150–200 mg/dL for diabetic patients. The PET study should be rescheduled if the serum glucose is greater than 200 mg/dL, and insulin should not be used to adjust the blood glucose level (*4*). The ACR recommends that a serum glucose analysis be performed before ^{18}F-FDG administration (*5*). The 2008 Netherlands protocol for standardization of multicenter ^{18}F-FDG PET studies suggested that the blood glucose level not be greater than 11 mmol/L (*6*). There was broad agreement among the Imaging Response Assessment Team sites that PET/CT studies should not be done if the glucose levels are more than 200 mg/dL (*10*). Blood glucose cutoff levels varied widely in the international survey and ranged from 150 to 250 mg/dL, with most sites (52%) accepting a cutoff of 200 mg/dL and 7% of sites reporting no cutoff level (*11*).

Prominent ^{18}F-FDG bowel uptake, which can compromise image quality, has been identified by multiple investigators with use of metformin (Fig. 2). Gontier et al. conducted a prospective study to determine the impact of antidiabetic medications on ^{18}F-FDG bowel uptake in type 2 diabetic patients (*33*). They compared the ^{18}F-FDG bowel uptake in 3 groups: type 2 diabetic patients on metformin, patients on oral antidiabetic treatments other than metformin, and a nondiabetic control group. They found that ^{18}F-FDG bowel uptake was significantly higher in patients treated with metformin than in the control group ($P < 0.0001$), although there was not a significant difference between patients treated with antidiabetic medications other than metformin and the control group. They concluded that metformin significantly increases ^{18}F-FDG uptake in the colon and to a lesser extent in the small intestine.

Several published studies have evaluated the effect of stopping metformin before the PET study and its impact on ^{18}F-FDG uptake. Ozulker et al. studied type 2 diabetic patients who underwent 2 PET studies, one while on metformin and the other after replacing metformin with another oral antidiabetic medication for 3 d before the second PET study (98 $\pm$ 7 d after the first PET study) (*34*). They found that the increased ^{18}F-FDG uptake in the bowel on the first PET study was significantly less on the second study after metformin had been stopped.

Additionally, Oh et al. studied 4 groups of patients: diabetic patients who continued metformin (group A1), diabetic patients who stopped metformin 2 d before the study (group A2), diabetic patients on a regimen that did not in-

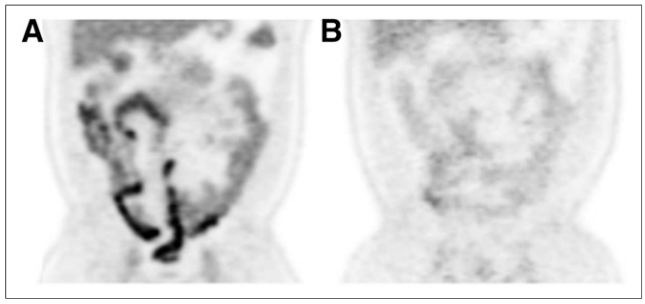

FIGURE 2. Effect of metformin on intestinal ^{18}F-FDG uptake. (A) Coronal ^{18}F-FDG PET image of diabetic patient while on metformin demonstrates prominent bowel activity. (B) Prior ^{18}F-FDG PET study of same patient while not on metformin shows only mild tracer activity in bowel.

clude metformin (group B), and nondiabetic individuals, who served as controls (group C) (*35*). In addition, 10 diabetic patients underwent 2 consecutive PET/CT scans before and after the discontinuation of metformin and the mean intestinal ^{18}F-FDG uptake decreased by 64% without significant changes in the blood glucose level. The high intestinal ^{18}F-FDG uptake in group A1 was significantly reduced in group A2 ($P < 0.001$). There were no significant differences in intestinal uptake among groups A2, B, and C. No statistically significant differences were noted in the blood glucose levels among the 3 groups of diabetic patients ($P > 0.9$).

In a written communication (Gholam Reza Berenji, 2013), the author of an abstract presented at the SNMMI 2013 midwinter meeting (*36*) looked into the effects of peroxisome proliferator-activated receptor–γ agonists (pioglitazone HCl, 30 mg, or rosiglitazone maleate, 8 mg tablets) on ^{18}F-FDG uptake and concluded that there was no significant difference in liver uptake, blood pool uptake, and liver–to–blood pool ratio between type 2 diabetic patients on the agonists and those not on them. The author concluded that peroxisome proliferator-activated receptor–γ agonists do not interfere with ^{18}F-FDG uptake and need not be withheld before an ^{18}F-FDG PET/CT study.

ENVIRONMENTAL CONDITIONS AND PREMEDICATIONS

Prominent ^{18}F-FDG uptake within brown adipose tissue (BAT) (Fig. 3), which normally has a role in nonshivering thermogenesis, can potentially mask or mimic malignant lesions. BAT is also postulated to be protective against diabetes and obesity (*37*). Other known predictors of the presence of BAT uptake include age (younger), sex (female), body mass index (lower), and maximum outdoor temperature (lower) (*38*). Cold exposure is known to stimulate BAT via an adrenergic mechanism (*18*), which is more pronounced during fasting (*39*). Therefore, to minimize activation of BAT, patients should avoid cold exposure for 2 d before the study and avoid air conditioning on the day of the study. During travel to the PET/CT clinic, they should keep the car windows rolled up and, if necessary, use the car heater on cool days. Patients also should wear warm clothing including long pants or slacks, long sleeves in summer (no shorts or tank tops), and, on cold or even slightly cool days, a sweater, jacket, and cap (*40,41*). We also maintain a warm room temperature (minimum, 75°F) and provide warm blankets to patients during the uptake period. The SNMMI and others recommend that patients be kept in a quiet, dimly lit, warm room 30–60 min before the injection of ^{18}F-FDG (*2,18*). Patients should remain as calm as possible, without moving excessively or talking during the uptake phase, to minimize muscle uptake. Other agents and medications such as nicotine and sympathomimetics (ephedrine) are also known to activate BAT and should be withheld before the PET study (*42*). Williams and Kolodny were the first to demonstrate a decrease in the frequency of ^{18}F-FDG uptake in BAT by incorporating a high-fat, very low carbohydrate, protein-permitted diet 3–5 h before ^{18}F-FDG injection (*43*).

Benzodiazepines have been successfully used before PET imaging to relieve anxiety in claustrophobic patients and to relax skeletal muscles. However, the efficacy of benzodiazepines in reducing BAT uptake is questionable (*44,45*). A randomized controlled trial evaluating the effects of oral diazepam on the neck and upper chest muscles and on BAT uptake found no significant difference between a group of patients receiving 5 mg of oral diazepam and a group receiving a placebo (*46*). Gelfand et al. have also shown a reduction of interfering ^{18}F-FDG uptake in BAT with use of intravenous fentanyl premedication (*44*). Other investigators have demonstrated successful reduction of BAT uptake with β-blockers. Soderlund et al., Parysow et al., and Agrawal et al. demonstrated complete or near-complete resolution

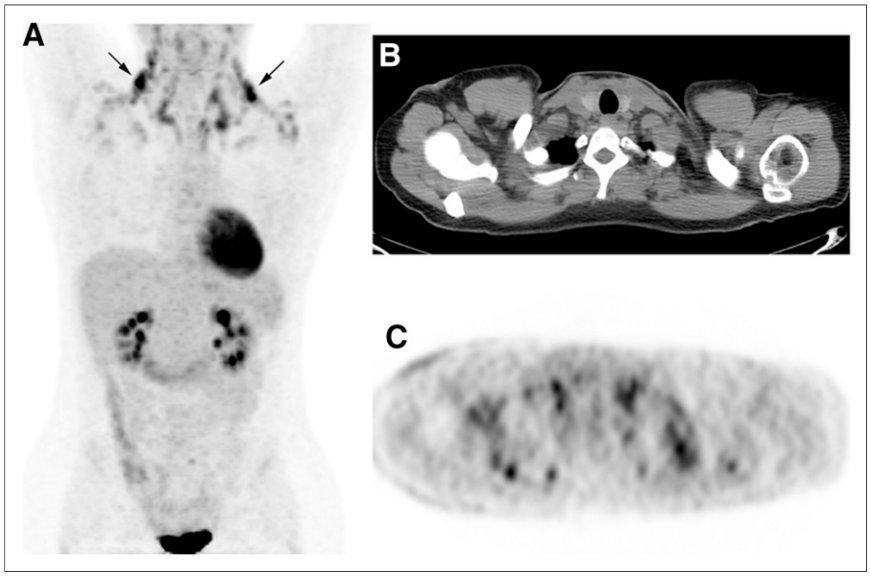

FIGURE 3. (A) Maximum-intensity-projection image shows intense bilateral radiotracer activity (arrows) in cervical and supraclavicular regions secondary to activation of BAT. (B and C) Axial non–contrast-enhanced CT (B) and PET (C) images localize radiotracer activity to cervical adipose tissue.

of BAT uptake with use of 80 mg, 20 mg, and 40 mg of oral propranolol, respectively, 1–2 h before ^{18}F-FDG injection (*47–49*). We do not routinely administer sedatives or β-blockers in our PET clinic. The SNMMI suggests the administration of lorazepam or diazepam before the injection of ^{18}F-FDG to reduce uptake by BAT or skeletal muscle or the administration of β-blockers to reduce uptake by brown fat (*2*). The EANM states that there is no reason for routine use of sedatives and suggests that sedatives such as short-acting benzodiazepines be considered in patients with head and neck tumors to reduce muscle uptake or in anxious claustrophobic patients, whereas in children, sedation may be required depending on the age of the child and the type of tumor (*3*). The NCI, at the discretion of the clinician, recommends the administration of a sedative such as diazepam in patients who are extremely anxious or in whom the area of interest is the head and neck (*4*). In patients with a history or suspicion of head and neck tumors, the NCI recommends that a benzodiazepine or similar sedative, if not medically contraindicated, be administered orally or intravenously approximately 30 min before injection of the ^{18}F-FDG to ensure a degree of relaxation of the neck muscles. The ACR suggests premedication for anxiety if indicated (*5*).

TIMING OF PET/CT

The optimal timing of ^{18}F-FDG PET for assessing response after initiating treatment has yet to be clearly determined. Confounding variables related to the timing of the PET study that have a potential impact on image interpretation include inflammation after surgery and radiation, bone marrow effects from use of chemotherapies or colony-stimulating factors, and the effects of chemotherapy on tumor metabolism and macrophage impairment. Acute inflammatory changes with subsequent alterations in ^{18}F-FDG uptake in both tumor and surrounding tissue have been documented after completion of radiation therapy (*50*). EANM guidelines recommend that the optimum interval between the last chemotherapy cycle and the PET study be at least 10 d, whereas it is best to wait for 3 mo after radiotherapy (*3*). The NCI working group (*4*) suggests that posttreatment imaging be performed at least 2 wk after the end of a specific chemotherapy cycle and 6–8 wk or longer after radiation therapy. The Netherlands protocol for standardization and quantification of ^{18}F-FDG whole-body PET studies in multicenter trials suggests that an interval of 4 mo may be required after completion of radiation treatment (*6*). The timing of ^{18}F-FDG PET/CT after radiofrequency ablation of lung tumors was determined to be at least 3 mo by Higaki et al. (*51*). The optimal timing of ^{18}F-FDG PET after surgery is controversial as well. In patients with squamous cell carcinoma of the head and neck, Zimmer et al. suggest that ^{18}F-FDG PET imaging be performed no sooner than 2–3 mo after surgery with or without chemoradiation to decrease the number of false-positive findings secondary to inflammation (*52*). However, other investigators have concluded that despite a high rate of false-positive findings, an earlier postoperative PET/CT examination (median time between surgery and PET/CT, 28 d; range, 13–75 d) significantly changed the adjuvant treatment plan in 15.4% of patients with head and neck cancer (*53*). In the case of radiation therapy, this delay allows patterns of activity and parenchymal change to stabilize, although increased activity may persist up to 15 mo after the end of radiation therapy (*54*). To minimize treatment-related false-negative and -positive findings, we suggest that PET studies be done at least 2 wk after the end of the last chemotherapy cycle, 6–8 wk after surgery, and 12 wk after radiation therapy.

CONCLUSION

^{18}F-FDG PET/CT is a frequently used imaging modality in the evaluation of patients with cancer. There is considerable variability in the PET/CT procedure worldwide. Strict adherence to standardized procedures and protocols is an essential requirement toward obtaining good-quality images and ensuring reproducibility across different clinic sites. This review has summarized relevant aspects of patient preparation as outlined by major societies and has proposed a standard patient preparation protocol that can easily be incorporated into daily clinical practice.

REFERENCES

1. *2012 PET Market Summary Report.* Greenbelt, MD: IMV; 2012.
2. Delbeke D, Coleman RE, Guiberteau MJ, et al. Procedure guideline for tumor imaging with ^{18}F-FDG PET/CT 1.0. *J Nucl Med.* 2006;47:885–895.
3. Boellaard R, O'Doherty MJ, Weber WA, et al. FDG PET and PET/CT: EANM procedure guidelines for tumour PET imaging—version 1.0. *Eur J Nucl Med Mol Imaging.* 2010;37:181–200.
4. Shankar LK, Hoffman JM, Bacharach S, et al. Consensus recommendations for the use of ^{18}F-FDG PET as an indicator of therapeutic response in patients in National Cancer Institute Trials. *J Nucl Med.* 2006;47:1059–1066.
5. ACR–SPR Practice Guideline for performing FDG-PET/CT in Oncology. American College of Radiology Web site. http://www.acr.org/~/media/71B746780F934F6D8A1BA5CCA5167EDB.pdf. Published 2007. Amended 2009. Revised 2012. Accessed January 2, 2014.
6. Boellaard R, Oyen WJ, Hoekstra CJ, et al. The Netherlands protocol for standardisation and quantification of FDG whole body PET studies in multi-centre trials. *Eur J Nucl Med Mol Imaging.* 2008;35:2320–2333.
7. Jacene HA, Leboulleux S, Baba S, et al. Assessment of interobserver reproducibility in quantitative ^{18}F-FDG PET and CT measurements of tumor response to therapy. *J Nucl Med.* 2009;50:1760–1769.
8. Westerterp M, Pruim J, Oyen W, et al. Quantification of FDG PET studies using standardised uptake values in multi-centre trials: effects of image reconstruction, resolution and ROI definition parameters. *Eur J Nucl Med Mol Imaging.* 2007;34:392–404.
9. Velasquez LM, Boellaard R, Kollia G, et al. Repeatability of ^{18}F-FDG PET in a multicenter phase I study of patients with advanced gastrointestinal malignancies. *J Nucl Med.* 2009;50:1646–1654.
10. Graham MM, Badawi RD, Wahl RL. Variations in PET/CT methodology for oncologic imaging at U.S. academic medical centers: an imaging response assessment team survey. *J Nucl Med.* 2011;52:311–317.
11. Beyer T, Czernin J, Freudenberg LS. Variations in clinical PET/CT operations: results of an international survey of active PET/CT users. *J Nucl Med.* 2011;52:303–310.
12. Brechtel K, Klein M, Vogel M, et al. Optimized contrast-enhanced CT protocols for diagnostic whole-body ^{18}F-FDG PET/CT: technical aspects of single-phase versus multiphase CT imaging. *J Nucl Med.* 2006;47:470–476.
13. Groves AM, Kayani I, Dickson JC, et al. Oral contrast medium in PET/CT: should you or shouldn't you? *Eur J Nucl Med Mol Imaging.* 2005;32:1160–1166.

14. Berthelsen AK, Holm S, Loft A, Klausen TL, Andersen F, Hojgaard L. PET/CT with intravenous contrast can be used for PET attenuation correction in cancer patients. *Eur J Nucl Med Mol Imaging.* 2005;32:1167–1175.
15. Pfannenberg AC, Aschoff P, Brechtel K, et al. Value of contrast-enhanced multiphase CT in combined PET/CT protocols for oncological imaging. *Br J Radiol.* 2007;80:437–445.
16. Dilsizian MV, Bacharach PSL, Beanlands MRS, et al. PET myocardial perfusion and metabolism clinical imaging. *J Nucl Cardiol.* 2009;16:651. http://www.asnc.org/imageuploads/ImagingGuidelinesPETJuly2009.pdf. Published 2009. Accessed January 15, 2014.
17. Shreve P, Townsend DW, eds. *Clinical PET/CT in Radiology: Integrated Imaging in Oncology.* New York, NY: Springer; 2011.
18. Cohade C. Altered biodistribution on FDG-PET with emphasis on brown fat and insulin effect. *Semin Nucl Med.* 2010;40:283–293.
19. Gosmanov AR, Goorha S, Stelts S, Peng L, Umpierrez GE. Management of hyperglycemia in diabetic patients with hematologic malignancies during dexamethasone therapy. *Endocr Pract.* 2013;19:231–235.
20. Baldwin D, Apel J. Management of hyperglycemia in hospitalized patients with renal insufficiency or steroid-induced diabetes. *Curr Diab Rep.* 2013;13:114–120.
21. Torizuka T, Clavo AC, Wahl RL. Effect of hyperglycemia on in vitro tumor uptake of tritiated FDG, thymidine, L-methionine and L-leucine. *J Nucl Med.* 1997;38:382–386.
22. Wahl RL, Henry CA, Ethier SP. Serum glucose: effects on tumor and normal tissue accumulation of 2-[F-18]-fluoro-2-deoxy-D-glucose in rodents with mammary carcinoma. *Radiology.* 1992;183:643–647.
23. Diederichs CG, Staib L, Glatting G, Beger HG, Reske SN. FDG PET: elevated plasma glucose reduces both uptake and detection rate of pancreatic malignancies. *J Nucl Med.* 1998;39:1030–1033.
24. Lindholm P, Minn H, Leskinen-Kallio S, Bergman J, Ruotsalainen U, Joensuu H. Influence of the blood glucose concentration on FDG uptake in cancer: a PET study. *J Nucl Med.* 1993;34:1–6.
25. Boellaard R. Standards for PET image acquisition and quantitative data analysis. *J Nucl Med.* 2009;50(suppl 1):11S–20S.
26. Turcotte E, Leblanc M, Carpentier A, Benard F. Optimization of whole-body positron emission tomography imaging by using delayed 2-deoxy-2-[F-18]fluoro-D-glucose injection following I.V. insulin in diabetic patients. *Mol Imaging Biol.* 2006;8:348–354.
27. Caobelli F, Pizzocaro C, Paghera B, Guerra UP. Proposal for an optimized protocol for intravenous administration of insulin in diabetic patients undergoing ^{18}F-FDG PET/CT. *Nucl Med Commun.* 2013;34:271–275.
28. Roy FN, Beaulieu S, Boucher L, Bourdeau I, Cohade C. Impact of intravenous insulin on ^{18}F-FDG PET in diabetic cancer patients. *J Nucl Med.* 2009;50:178–183.
29. Nakatani K, Nakamoto Y, Togashi K. Risk factors for extensive skeletal muscle uptake in oncologic FDG-PET/CT for patients undergoing a 4-h fast. *Nucl Med Commun.* 2012;33:648–655.
30. Büsing KA, Schonberg SO, Brade J, Wasser K. Impact of blood glucose, diabetes, insulin, and obesity on standardized uptake values in tumors and healthy organs on ^{18}F-FDG PET/CT. *Nucl Med Biol.* 2013;40:206–213.
31. Niederkohr RD, Quon A. No apparent alteration of F-18 FDG biodistribution when injected shortly after insulin glargine. *Clin Nucl Med.* 2007;32:302–303.
32. Schmeltz LR. Safe insulin use in the hospital setting. *Hosp Pract (1995).* 2009;37:51–59.
33. Gontier E, Fourme E, Wartski M, et al. High and typical ^{18}F-FDG bowel uptake in patients treated with metformin. *Eur J Nucl Med Mol Imaging.* 2008;35:95–99.
34. Ozülker T, Ozülker F, Mert M, Ozpacaci T. Clearance of the high intestinal ^{18}F-FDG uptake associated with metformin after stopping the drug. *Eur J Nucl Med Mol Imaging.* 2010;37:1011–1017.
35. Oh JR, Song HC, Chong A, et al. Impact of medication discontinuation on increased intestinal FDG accumulation in diabetic patients treated with metformin. *AJR.* 2010;195:1404–1410.
36. Berenji GR. The effect of peroxisome proliferator-activated receptor-γ (PPAR-γ) agonists on [^{18}F]-fluorodeoxyglucose(18-F FDG)uptake. Paper presented at: 2012 Mid-Winter Meeting of the Society of Nuclear Medicine and Molecular Imaging; January 26–29, 2012; Orlando, Florida.
37. Jacene HA, Cohade CC, Zhang Z, Wahl RL. The relationship between patients' serum glucose levels and metabolically active brown adipose tissue detected by PET/CT. *Mol Imaging Biol.* 2011;13:1278–1283.
38. Pace L, Nicolai E, D'Amico D, et al. Determinants of physiologic ^{18}F-FDG uptake in brown adipose tissue in sequential PET/CT examinations. *Mol Imaging Biol.* 2011;13:1029–1035.
39. Vrieze A, Schopman JE, Admiraal WM, et al. Fasting and postprandial activity of brown adipose tissue in healthy men. *J Nucl Med.* 2012;53:1407–1410.
40. Garcia CA, Van Nostrand D, Atkins F, et al. Reduction of brown fat 2-deoxy-2-[F-18]fluoro-D-glucose uptake by controlling environmental temperature prior to positron emission tomography scan. *Mol Imaging Biol.* 2006;8:24–29.
41. Garcia C, Bandaru V, Van Nostrand D, et al. Effective reduction of brown fat FDG uptake by controlling environmental temperature prior to PET scan: an expanded case series. *Mol Imaging Biol.* 2010;12:652–656.
42. Baba S, Tatsumi M, Ishimori T, Lilien DL, Engles JM, Wahl RL. Effect of nicotine and ephedrine on the accumulation of ^{18}F-FDG in brown adipose tissue. *J Nucl Med.* 2007;48:981–986.
43. Williams G, Kolodny GM. Method for decreasing uptake of ^{18}F-FDG by hypermetabolic brown adipose tissue on PET. *AJR.* 2008;190:1406–1409.
44. Gelfand MJ, O'Hara SM, Curtwright LA, Maclean JR. Pre-medication to block [^{18}F]FDG uptake in the brown adipose tissue of pediatric and adolescent patients. *Pediatr Radiol.* 2005;35:984–990.
45. Tatsumi M, Engles JM, Ishimori T, Nicely O, Cohade C, Wahl RL. Intense ^{18}F-FDG uptake in brown fat can be reduced pharmacologically. *J Nucl Med.* 2004; 45:1189–1193.
46. Sturkenboom MG, Hoekstra OS, Postema EJ, Zijlstra JM, Berkhof J, Franssen EJ. A randomised controlled trial assessing the effect of oral diazepam on ^{18}F-FDG uptake in the neck and upper chest region. *Mol Imaging Biol.* 2009;11:364–368.
47. Söderlund V, Larsson SA, Jacobsson H. Reduction of FDG uptake in brown adipose tissue in clinical patients by a single dose of propranolol. *Eur J Nucl Med Mol Imaging.* 2007;34:1018–1022.
48. Parysow O, Mollerach AM, Jager V, Racioppi S, San Roman J, Gerbaudo VH. Low-dose oral propranolol could reduce brown adipose tissue F-18 FDG uptake in patients undergoing PET scans. *Clin Nucl Med.* 2007;32:351–357.
49. Agrawal A, Nair N, Baghel NS. A novel approach for reduction of brown fat uptake on FDG PET. *Br J Radiol.* 2009;82:626–631.
50. Castellucci P, Zinzani P, Nanni C, et al. ^{18}F-FDG PET early after radiotherapy in lymphoma patients. *Cancer Biother Radiopharm.* 2004;19:606–612.
51. Higaki F, Okumura Y, Sato S, et al. Preliminary retrospective investigation of FDG-PET/CT timing in follow-up of ablated lung tumor. *Ann Nucl Med.* 2008;22:157–163.
52. Zimmer LA, Branstetter BF, Nayak JV, Johnson JT. Current use of ^{18}F-fluorodeoxyglucose positron emission tomography and combined positron emission tomography and computed tomography in squamous cell carcinoma of the head and neck. *Laryngoscope.* 2005;115:2029–2034.
53. Shintani SA, Foote RL, Lowe VJ, Brown PD, Garces YI, Kasperbauer JL. Utility of PET/CT imaging performed early after surgical resection in the adjuvant treatment planning for head and neck cancer. *Int J Radiat Oncol Biol Phys.* 2008;70:322–329.
54. Larici AR, del Ciello A, Maggi F, et al. Lung abnormalities at multimodality imaging after radiation therapy for non-small cell lung cancer. *Radiographics.* 2011;31:771–789.