

Impact of Intravenous Insulin on ^{18}F -FDG PET in Diabetic Cancer Patients

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The aims of this study were to evaluate the effectiveness of a standardized insulin protocol in reducing glycemia, review ^{18}F -FDG biodistribution with such a protocol, and assess its clinical impact. **Methods:** Sixty-three patients with glycemia greater than 10 mmol/L received insulin doses intravenously according to a standardized protocol. One hundred six consecutive euglycemic patients (<6.2 mmol/L) served as controls. ^{18}F -FDG biodistribution was evaluated by 2 experienced PET readers on a 5-point visual scale based on muscular uptake. The 63 patients who received insulin were divided into insulin subgroup A, with adequate biodistribution (score 0, 1, or 2) and insulin subgroup B, with altered biodistribution (score 3 or 4). ^{18}F -FDG biodistribution was also evaluated semiquantitatively by standardized uptake value (SUV) measurements over the liver, gluteal muscles, and myocardium. Clinical impact (complications and diagnostic accuracy) was assessed by follow-up. **Results:** Glycemia decreased from 13 ± 2 to 7 ± 2 mmol/L after insulin injection. Images showed significantly more muscular uptake in patients who received insulin than in the control group (scores 1.6 ± 1.5 vs. 0.4 ± 0.6 , $P < 0.05$). Twenty-five percent of insulin patients studied had altered biodistribution (insulin subgroup B). The two most important factors increasing muscular uptake were the time interval between insulin and ^{18}F -FDG injection (mean in insulin subgroup A, 80.2 ± 17 min; mean in insulin subgroup B, 65.7 ± 10 min; $P < 0.01$) and the glycemia interval decrease after insulin injection (mean in insulin subgroup A, 5.3 ± 2.6 mmol/L; mean in insulin subgroup B, 7.6 ± 1.8 mmol/L; $P < 0.01$). In insulin subgroup B, mean hepatic SUV was lower (1.3 ± 0.4 vs. 2.1 ± 0.4 , $P < 0.01$) and mean muscular SUV was higher (1.8 ± 0.1 vs. 0.9 ± 0.01 , $P < 0.01$). Of the 63 patients who received insulin, 6 had hypoglycemia, but only 2 were symptomatic. No patient had severe complications causing permanent disability. **Conclusion:** A standardized protocol of intravenous insulin before ^{18}F -FDG injection in diabetic cancer patients was safe and effective in reducing glycemia. Acceptable ^{18}F -FDG biodistribution was obtained in 75% of patients receiving insulin. In addition to visually increased muscular uptake, low hepatic ^{18}F -FDG uptake was a good indicator of altered biodistribution.

Key Words: diabetes; insulin; hyperglycemia; FDG; PET; endocrinology; oncology

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The staging and follow-up of many cancers are now routinely performed with ^{18}F -FDG PET. Unfortunately, hyperglycemia, defined as fasting glycemia greater than 7 mmol/L (126 mg/dL), may lower the sensitivity of this test (1). Diabetes is reaching epidemic proportions in North America. Its prevalence increases with age (2), and the same is true for cancer.

Acute hyperglycemia is a well-documented factor that reduces tumoral ^{18}F -FDG uptake (3,4) and augments muscular uptake (1), but this effect has mostly been demonstrated with glucose-loading studies (1,5). It has been reported that hyperglycemia decreases pancreatic cancer detection by ^{18}F -FDG PET (6). The effect of chronic hyperglycemia on ^{18}F -FDG PET performance is more controversial. Mild to moderate diabetes does not influence PET efficacy in patients with untreated locally advanced primary cancer or clinically curable recurrent cervical carcinoma (7), and ^{18}F -FDG uptake in pulmonary cancer is not affected in well-controlled diabetes (8). However, diabetes has been associated with reduced ^{18}F -FDG uptake by pulmonary cancer (9).

Published data on the use of insulin to normalize glycemia in diabetic cancer patients before ^{18}F -FDG PET are scarce. ^{18}F -FDG, given 30 min after insulin injection, had a negative impact on ^{18}F -FDG tumoral uptake in an animal study (10). In clinical patients, an intravenous bolus of insulin at least 60 min before ^{18}F -FDG injection safely reduced glycemia without compromising image quality or lung tumor standardized uptake values (SUVs) (11). The available literature suggests that most patients (diabetic or nondiabetic) with glycemia less than 10 mmol/L (180 mg/dL) have adequate ^{18}F -FDG biodistribution. The Society of Nuclear Medicine guidelines for PET/CT recommend that ^{18}F -FDG should not be injected when glycemia is above 8.3–11.1 mmol/L (150–200 mg/dL), and if insulin is injected to lower glycemia, ^{18}F -FDG administration should be delayed (12). The European Association of Nuclear Medicine recommends that glycemia should ideally not exceed

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7.2 mmol/L (130 mg/dL), and the test should be postponed if glycemia is higher than 11.1 mmol/L (200 mg/dL) (13).

The objectives of this study were to evaluate the effectiveness of a standardized intravenous insulin injection protocol that normalizes glycemia, to examine its clinical impact in terms of safety and diagnostic accuracy, and to assess its influence on ^{18}F -FDG biodistribution.

MATERIALS AND METHODS

Patient Selection and Preparation

The charts of 4,593 consecutive ^{18}F -FDG PET patients were reviewed. Glycemia in 71 patients (1.5%) was above 10 mmol/L. Among these patients, 63 (1.4%) received short-acting intravenous insulin (Humulin R; Eli Lilly & Co.) and comprised the insulin group. Insulin was administered according to a standardized protocol (2 units for glycemia of 10.0–12.0 mmol/L, 3 units for glycemia of 12.1–14.0 mmol/L, and 4–6 units for glycemia of 14.1 mmol/L and above) to reach a glycemia lower than 10.0 mmol/L. Glycemia was measured before insulin injection, at 30 and 60 min after insulin injection, and before the patient left the department. If glycemia showed only minimal reduction at 30 min and was still above 10.0 mmol/L, a second insulin dose was given. Hypoglycemia was treated with an oral glucose solution. ^{18}F -FDG was injected at least 60 min after the last insulin administration.

The ^{18}F -FDG PET studies of the 63 consecutive patients who received insulin were reviewed. One hundred six consecutive euglycemic (glycemia < 6.2 mmol/L) nondiabetic patients who came to our department in the month preceding the gathering of the data for this retrospective study served as the control group and were evaluated according to the same qualitative and semiquantitative criteria.

All patients were instructed to fast for 4–6 h before the tests; to eat lightly the day before, using a low-carbohydrate diet; and to withhold short-acting subcutaneous insulin injections the day of PET. Every other medication, including oral antihyperglycemic agents, was allowed. Known diabetic patients were instructed to have their glycemia well controlled in the days preceding the examination. They were scheduled early in the morning.

Study Acquisition

PET was performed from the base of the skull through the proximal femurs approximately 60 min after ^{18}F -FDG injection (7.5 MBq/kg intravenously) on a 2-dimensional bismuth germanate scanner (Advance NXi; GE Healthcare). Emission data were collected at 5 min of emission per bed position on a 128 × 128 pixel matrix, and transmission data were collected at 3 min of emission per bed position, using a ^{68}Ge source for attenuation correction and a gaussian filter of 8 mm in full width at half maximum. Images were reconstructed with an ordered-subsets expectation maximization iterative algorithm (2 iterations, 14 subsets) and segmented attenuation correction.

Insulin Impact

The ability of intravenous insulin to normalize glycemia was evaluated. Although the normal accepted range of fasting glycemia was 4.0–7.0 mmol/L, a value of up to 10.0 mmol/L was considered acceptable for the examination. Side effects with signs and symptoms of hypoglycemia were recorded. Hypoglycemia was defined as glycemia of 3.5 mmol/L or less. When follow-up was available, the rate of false-negative PET interpretations was recorded among patients who received insulin.

Image Analysis

^{18}F -FDG biodistribution was graded by 2 experienced PET readers on a 5-point scale: normal biodistribution (score 0); mild muscular uptake (score 1); muscular uptake involving more than 1 muscle group (score 2); diffuse muscular uptake of moderate intensity (score 3); and diffuse, intense muscular uptake resulting in a nondiagnostic examination (score 4). Discordant gradings were resolved by consensus. Insulin patients were divided into subgroup A, with adequate biodistribution (score 0, 1, or 2; Fig. 1), and subgroup B, with altered biodistribution (score 3 or 4; Fig. 2).

Maximal and mean SUV was evaluated semiquantitatively on transaxial slices of the gluteal muscles, liver, and myocardium. SUV was not corrected for glycemia. Gluteal muscles were chosen as the measurement site of striated muscular uptake because they were large enough to ensure that the region of interest included only muscle and facilitated reproducibility. A circular 3-cm-diameter region of interest centered on the region with maximal uptake was obtained for the gluteal muscles bilaterally. A 4-cm-diameter region of interest centered on the middle region of a transverse slice of the right lobe of the liver was generated. Finally, SUV was measured in a 1-cm-diameter region of interest centered on the myocardium region with maximal uptake. These measures provided an objective evaluation of insulin impact on ^{18}F -FDG biodistribution.

Statistical Analysis

The unpaired *t* test was used to compare SUV and scores between groups. The biodistribution score was correlated with different clinical parameters and SUVs by regression analysis. A *P* value of less than 0.05 was considered statistically significant. No correction for multiple testing was performed. Unless otherwise specified, all data are reported as mean ± SD.

RESULTS

Demographic characteristics were significantly different between the insulin and control groups in terms of age (65.3 vs. 56.5 y old), weight (81.2 vs. 69.9 kg), and initial glycemia (13.0 ± 2.2 vs. 5.3 ± 0.5 mmol/L). The only significant difference between insulin subgroups A and B was body weight (84.6 vs. 68.9 kg, *P* < 0.01). Most insulin patients were evaluated for lung cancer (46%), followed by gastrointestinal cancers (24%), genitourinary cancer (8%), breast

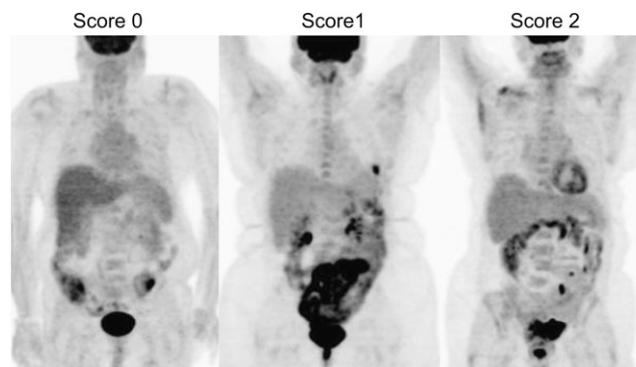
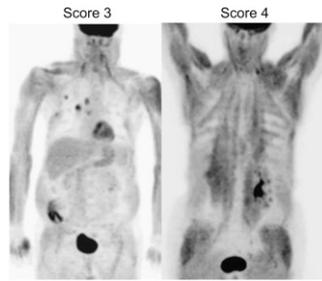


FIGURE 1. Maximum-intensity-projection images of insulin subgroup A: patients with adequate biodistribution (score 0, 1, or 2).

FIGURE 2. Maximum-intensity-projection images of insulin subgroup B: patients with altered biodistribution (score 3 or 4).



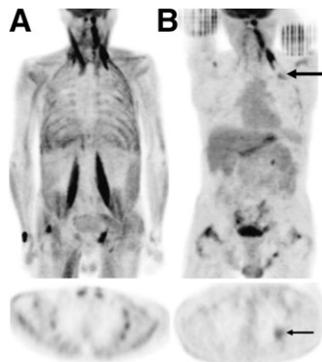
cancer (5%), and lymphoma (5%). Sixty (95%) had type II diabetes. One patient had type I diabetes, and in 2 patients the diagnosis of diabetes was made in our department.

In patients receiving insulin, glycemia decreased from 13 ± 2 to 7 ± 2 mmol/L after insulin injection. Twenty-six patients (41.3%) had glycemia of 3.6–7.0 mmol/L, 25 (39.7%) of 7.1–10.0 mmol/L, and 6 (9.5%) still had glycemia above 10 mmol/L after insulin injection. Six other patients (9.5%) experienced hypoglycemia (as measured by a glucometer), but only 2 presented with symptoms, which were minor and resolved rapidly after administration of oral glucose solution. No patient had severe or long-term complications.

Forty-one patients (65%) with unavailable follow-up were referred from outside hospitals. Follow-up was based on available clinical, radiologic, and pathologic data, which could be retrieved in 20 patients. Among the 20 patients with available follow-up data, four ^{18}F -FDG PET studies were considered false-negative: 1 case of Langerhans cell histiocytosis (score 4), 1 of infracentimetric pulmonary metastases from a leiomyosarcoma (score 4), 1 of signet cell stomach carcinoma (score 1), and 1 of lung adenocarcinoma (score 4) (Fig. 3).

Fifteen discordant gradings were resolved by consensus. The grading differed by only 1 in each case. Seventy-five percent ($n = 47$) of ^{18}F -FDG PET scans of the insulin group patients showed adequate biodistribution (insulin subgroup A). All control patients had adequate biodistribution (Fig. 4). One of the factors most strongly associated with muscular uptake was the time interval between insulin and ^{18}F -FDG injections (Fig. 5A). The other important factor associated with muscular uptake was the glycemia decrease after insulin (Fig. 5B).

FIGURE 3. (A) Maximum-intensity-projection and transverse images of false-negative case with lung adenocarcinoma after insulin injection. (B) Lesion was clearly seen 1 wk later on MIP and transverse images in normoglycemic state without insulin injection (arrows in B).



A correlation was found between the biodistribution score and mean hepatic SUV, with a significant difference between insulin subgroups A (2.1 ± 0.4) and B (1.3 ± 0.4) ($P < 0.01$) (Fig. 6A). As expected, the association was very significant between the biodistribution score and gluteal muscular SUV ($r = 0.73$, $P < 0.00001$) and was significant between the insulin subgroups (Fig. 6B). The association with myocardial SUV was less significant. The results were comparable between insulin subgroup A and the control group.

No significant association was observed between muscular uptake and variables such as initial glycemia, total insulin dose, the number of insulin doses, and the delay between ^{18}F -FDG injection and the start of acquisition.

DISCUSSION

The proposed intravenous insulin protocol proved to be safe and effective in preparing diabetic cancer patients for oncologic ^{18}F -FDG PET studies. Seventy-five percent of patients showed adequate biodistribution after insulin injection, and only 1 proved to be falsely negative based on available follow-up data (the patient with signet cell stomach carcinoma). Moreover, the only case in which a false-negative result could be attributed to the insulin injection (the patient with lung adenocarcinoma) was easily identified because ^{18}F -FDG biodistribution was clearly altered (a patient from insulin subgroup B), resulting in a nondiagnostic study. The other false-negative cases included Langerhans cell histiocytosis, moderately differentiated leiomyosarcoma, and signet cell stomach cancer. These cancers are well known to have low ^{18}F -FDG avidity. Furthermore, the infracentimetric pulmonary metastases of the leiomyosarcoma were not even seen on follow-up PET performed a few days later with normoglycemia.

The examination did not have to be rescheduled for most diabetic cancer patients, even if glycemia was above 10 mmol/L. Rescheduling a PET scan results in diagnostic delays in view of the time necessary to optimize glycemia in diabetic patients in whom therapy is pending. Ideally, every diabetic patient should be contacted days before the PET examination to assess glycemia and, if necessary, more intensive treatment should be instituted to normalize it. Unfortunately, even with adequate recommendations, some patients will reach the department with elevated glycemia.

Although less well documented than acute hyperglycemia, chronic hyperglycemia is assumed to have a similar but smaller negative influence on tumoral uptake. No well-designed prospective, randomized clinical study has specifically addressed this issue. An *in vitro* investigation showed that ^{18}F -FDG uptake did not significantly change in human adenocarcinoma cells with chronic hyperglycemia (300 mg/dL), whereas acute hyperglycemia markedly reduced ^{18}F -FDG and thymidine uptake (14). This finding indicates that the ^{18}F -FDG tumoral uptake process in a chronic hyperglycemia setting is still not fully understood. Compensatory mechanisms may be involved. The level of glycemia and duration of the hyperglycemic state that will significantly

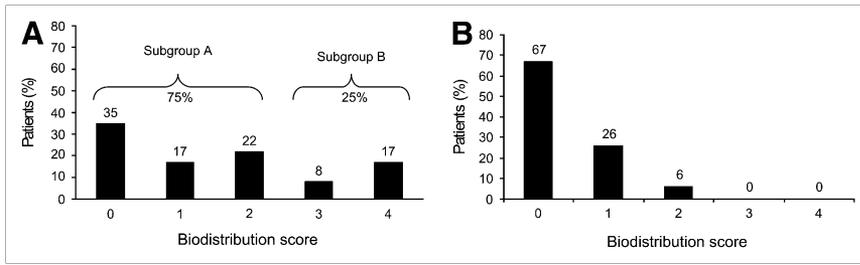


FIGURE 4. Biodistribution scores in insulin patients (1.6 ± 1.5) (A) were significantly different from those in control patients (0.4 ± 0.6 , $P < 0.05$) (B).

reduce ^{18}F -FDG uptake in cancer cells are not known. The Society of Nuclear Medicine and European Association of Nuclear Medicine guidelines are based on the principle of precaution and a paucity of literature. Few centers have introduced an insulin protocol. In our protocol, the threshold of 10 mmol/L was chosen because the literature shows no or only a small influence on SUV at this level and the frequency of intravenous insulin administration should be reduced to the minimum considering the potential complications. If the upper glycemia limit had been set to 7 mmol/L, 294 patients (6.4%) would have received insulin, instead of the 63 (1.4%) with a 10 mmol/L limit. This limit would have significantly increased the proportion of patients receiving insulin and resulted in a logistical burden.

A direct negative effect of insulin on tumoral uptake has never been demonstrated either. Insulin acts via glucose transporter (GLUT)–4 receptors present in muscles (myocardial and striated) and adipose tissue but has no significant effect on GLUT-1 and GLUT-3 receptors found in tumors. Hyperinsulinemic euglycemic clamping, although an established technique to optimize myocardial uptake, does not induce major changes in the glucose uptake of lymphomatous tissue (15). Torizuka et al. showed that although diabetes markedly impaired tumor targeting with ^{18}F -FDG, the judicious use of insulin in diabetic patients may improve tumor-to-nontumor uptake ratios in specific organs such as the liver or lungs but consistently reduce tumor-to-muscle ratios (16).

The effect of glycemia on inflammatory lesions is more controversial. Some have suggested that below a certain level,

an elevated glucose concentration might not have a negative effect on ^{18}F -FDG uptake in inflammatory cells, contrary to that observed in malignant disorders (3). For others, glucose loading has greater effects on ^{18}F -FDG uptake in inflammatory lesions than in tumors (17).

Many articles have evaluated muscular glucose physiology. Glucose transport and phosphorylation are altered by obesity (18) and diabetes (19). Kelley et al. found that phosphorylation was altered only in diabetic patients (20) and that it increased in a dose-responsive manner with insulin infusion (21). Williams et al. showed that glucose transport increased in response to insulin in lean and obese patients but not significantly in type 2 diabetic subjects. A dose-responsive pattern of glucose phosphorylation stimulation was observed in all groups but was lower in obese and type 2 diabetic patients (22). Weight loss (23), exercise training (24,25), rosiglitazone (26), and troglitazone (27) have all been shown to improve skeletal muscular ^{18}F -FDG uptake.

In the liver, glucose uptake is dependent on GLUT-2 receptors and is not saturable. Insulin stimulates uptake by upregulating glucokinase transcription and glycogen synthase activity and by inhibiting glucose-6-phosphatase and glycogen phosphorylase in hepatocytes (28). Glucokinase is postulated to be the rate-limiting step for glucose entry into the liver, and its activity has been shown to be decreased in liver biopsies from obese type 2 diabetic individuals (29). Moreover, in diabetic animals, defects of glucokinase activity and glycogen synthesis were partially reversed by normalization of glycemia, implicating glucose toxicity as a mechanism (29). The

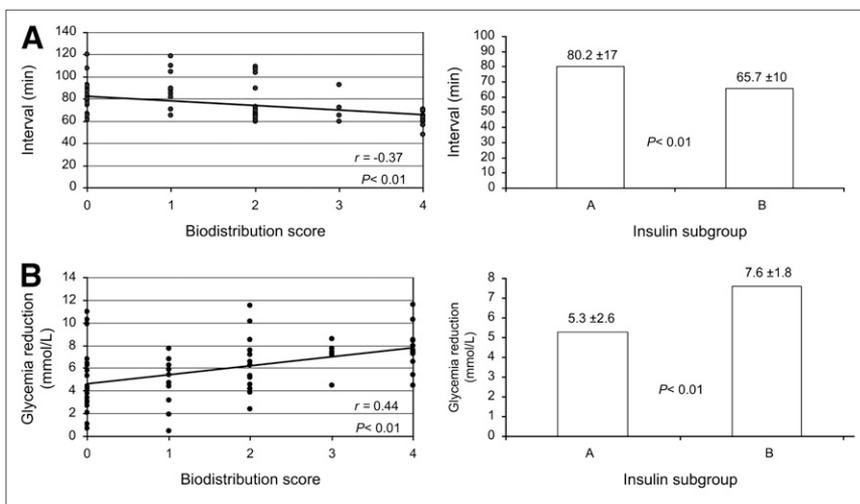
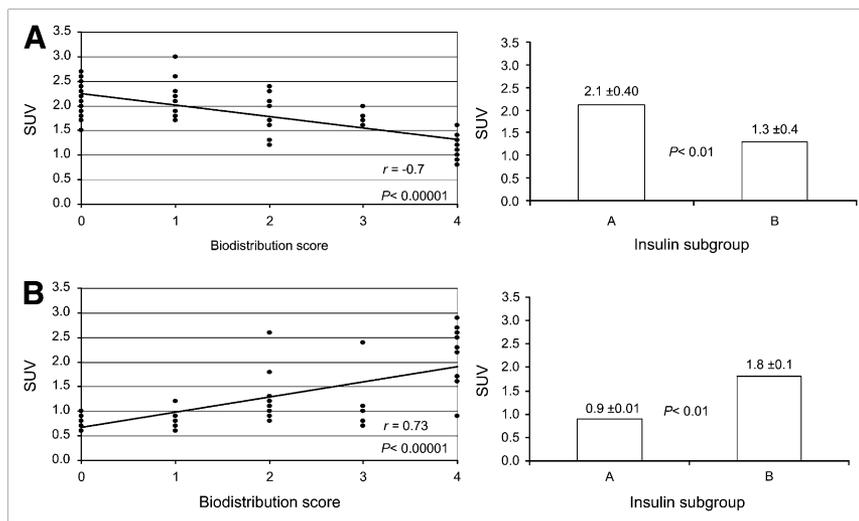


FIGURE 5. Time delay between insulin and ^{18}F -FDG injections (A) and glycemia reduction after insulin injection (B) was correlated with biodistribution score and was significantly different for insulin subgroups A and B.

FIGURE 6. Hepatic mean SUV (A) and gluteal muscular mean SUV (B) were correlated with biodistribution score and were significantly different for insulin subgroups A and B.



low hepatic ^{18}F -FDG uptake observed in our study is consistent with the findings of Iozzo et al. (28). In fact, hyperinsulinemia was found to enhance hepatic glucose influx and phosphorylation rates similarly in insulin-sensitive and -resistant patients, but the glucose phosphorylation-to-dephosphorylation ratio was significantly lower in patients with low insulin sensitivity (28). Metformin and rosiglitazone improved hepatic uptake in diabetic patients, likely by direct drug actions and better glycemic control (29). Moreover, the hepatic influx constant was inversely related to fasting glycemia and glycosylated hemoglobin in diabetic patients in a study by the same group (30). More recently, it was shown that nonesterified fatty acids impaired insulin-mediated hepatic glucose uptake and disposition in the liver (31). Another potential factor contributing to low hepatic uptake in patients receiving insulin is the diversion of ^{18}F -FDG to striated muscles, leaving less available for hepatic uptake. Low hepatic SUV can serve as an indicator of examination interpretability, considering that the liver is one of the structures showing the most constant activity on ^{18}F -FDG PET examinations. In the present study, mean hepatic SUVs were associated with overall visual biodistribution quality. A cutoff value of 1.6 could potentially distinguish patients with adequate from those with inadequate biodistribution.

Based on our results, a waiting period of at least 90 min should be observed after insulin injection. Turcotte et al. (11) used a 60-min delay and showed no negative impact of insulin on striated muscular (paraspinal and gluteal), myocardial, hepatic, pulmonary, and lung tumor SUV. Many factors could explain this situation. Their insulin protocol was more aggressive, with the threshold for insulin injection set at 7.0 mmol/L. Initial mean glycemia in their patient population was 9.7 ± 2.0 mmol/L, compared with 13 ± 2 mmol/L in ours. Most of their patients had initial glycemia below 10.0 mmol/L and an insulin-associated glycemia reduction of less than 5 mmol/L. This finding is significant, considering the impact of glycemia reduction on biodistribution quality observed in our study. The 90-min delay is empiric in that the half-life of

intravenous Humulin R insulin is 4 min. It can be expected that the insulin effect is terminated before 60 min. Renal and hepatic insufficiency were not accounted for but could contribute to the prolongation of insulin half-life. Another relevant finding is that one should not attempt to reduce glycemia if the initial glycemia is more than 15 mmol/L. Besides altering biodistribution and increasing the frequency of nondiagnostic studies, significant glycemia reduction can be deleterious by provoking hypokalemia.

A limitation of the present study is that fasting could not be controlled entirely. Inadequate fasting is the classic cause of diffuse muscular uptake. Two patients who received insulin were diagnosed with de novo diabetes, but we cannot exclude that they fasted insufficiently, although their PET studies demonstrated adequate biodistribution. A 4- to 6-h fast is generally recommended, although a longer fast is probably better. In an animal experiment, the negative effect of anesthetic agents on ^{18}F -FDG uptake was attenuated with a 20-h fasting period instead of 4 h (32), but this can hardly be implemented in human studies. The composition of the last meal was not documented, but a low-carbohydrate diet was recommended in written patient instructions before the examination. Another limitation is the low follow-up rate, which can be explained by the retrospective nature of the study and by the fact that many patients from outside hospitals were lost to follow-up.

The demonstration of an improvement in the diagnostic performance of ^{18}F -FDG PET with insulin administration is beyond the scope of our study, as it requires scans with and without insulin.

CONCLUSION

Intravenous insulin administration successfully decreased glycemia to acceptable levels in most cancer patients undergoing an ^{18}F -FDG PET examination, with a limited number being hypoglycemic. Acceptable ^{18}F -FDG biodistribution was obtained in 75% of patients receiving insulin. Tentative

recommendations include the administration of regular insulin intravenously in patients with glycemia between 10 and 15 mmol/L and rescheduling patients with glycemia above 15 mmol/L. An interval of 90 min between insulin and ^{18}F -FDG injections should be considered. Diffuse muscular uptake and a low hepatic SUV (less than 1.6) can be useful tools to determine that ^{18}F -FDG biodistribution is sufficiently altered to repeat the PET scan.

Considering the growing number of cancer patients affected by diabetes, the problem of elevated glycemia before an ^{18}F -FDG PET study will become increasingly common. Until more light is shed on the issue of chronic hyperglycemia, a pretest intravenous insulin injection in diabetic patients appears to be a careful and pragmatic approach. This investigation is a first attempt to clarify, in a clinical setting, which parameters most affect ^{18}F -FDG biodistribution after insulin injection. Prospective clinical trials should be undertaken to clarify the true clinical impact of insulin injection on ^{18}F -FDG studies.

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