Assessing the Effect of Various Blood Glucose Levels on ^{18}F-FDG Activity in the Brain, Liver, and Blood Pool

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Studies have extensively analyzed the effect of hyperglycemia on ^{18}F-FDG uptake in normal tissues and tumors. In this study, we measured SUV in the brain, liver, and blood pool in normoglycemia, hyperglycemia, and hypoglycemia to understand the effect of blood glucose on ^{18}F-FDG uptake and to develop a formula to correct SUV. **Methods:** Whole-body ^{18}F-FDG PET/CT images of adults were selected for analysis. Brain SUV_{max}, blood-pool SUV_{mean}, and liver SUV_{mean} were measured at blood glucose ranges of 61–70, 71–80, 81–90, 91–100, 101–110, 111–120, 121–130, 131–140, 141–150, 151–160, 161–170, 171–180, 181–190, 191–200, and 201 mg/dL and above. At each blood glucose range, 10 PET images were analyzed (total, 150). The mean (±SD) SUV of the brain, liver, and blood pool at each blood glucose range was calculated, and blood glucose and SUV curves were generated. Because brain and tumors show a high expression of glucose transporters 1 and 3, we generated an SUV correction formula based on percentage reduction in brain SUV_{max} with increasing blood glucose level. **Results:** Mean brain SUV_{max} gradually decreased with increasing blood glucose level, starting after a level of 110 mg/dL. The approximate percentage reduction in brain SUV_{max} was 20%, 35%, 50%, 60%, and 65% at blood glucose ranges of 111–120, 121–140, 141–160, 161–200, and 201 mg/dL and above, respectively. In the formula we generated, measured SUV_{max} is multiplied by a reduction factor of 1.25, 1.5, 2, 2.5, and 2.8 for the blood glucose ranges of 111–120, 121–140, 141–160, 161–200, and 201 mg/dL and above, respectively, to correct SUV. Brain SUV_{max} did not differ between hypoglycemic and normoglycemic patients ($P > 0.05$). SUV_{mean} in the blood pool and liver was lower in hypoglycemic patients ($P < 0.05$) and did not differ between hyperglycemic ($P > 0.05$) and normoglycemic patients. **Conclusion:** Hyperglycemia gradually reduces brain ^{18}F-FDG uptake, starting after a blood glucose level of 110 mg/dL. Hyperglycemia does not affect ^{18}F-FDG activity in the liver or blood pool. Hypoglycemia does not seem to affect brain ^{18}F-FDG uptake but appears to reduce liver and blood-pool activity. The simple formula we generated can be used to correct SUV in hyperglycemic adults in selected cases.

Key Words: blood glucose; ^{18}F-FDG; brain; liver; blood pool

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PET imaging with the radiolabeled glucose analog ^{18}F-FDG is commonly used in oncologic cases and is increasingly being used in neurologic, cardiac, and infectious and inflammatory diseases.

Glucose is transported across the plasma membrane into the cytosol by glucose transporters (GLUTs) (*1,2*). There are currently 14 isoforms of GLUTs, which differ in their tissue distribution. GLUT2 is expressed more in the liver, GLUT1 and GLUT3 are more commonly found in the brain, and GLUT4 is found mainly in insulin-sensitive tissues such as cardiac and skeletal muscular tissues and fat. The other normal tissues express various other GLUT isoforms. Cancer cells usually express GLUT1 and GLUT3, although certain cancer types may show expression of other isoforms of GLUTs (*1*).

Once taken up by the cells, ^{18}F-FDG is phosphorylated into ^{18}F-FDG-6-phosphate by hexokinase or glucokinase enzyme. ^{18}F-FDG-6-phosphate is mainly trapped in the cells, as it minimally undergoes subsequent metabolism (glycolysis or the tricarboxylic acid cycle) and its dephosphorylation rate is slow. Dephosphorylation is particularly low or absent in tumors (*3*). However, in liver, after being taken up by the cells, ^{18}F-FDG is rapidly released, which is believed to be due to high glucose-6-phosphatase activity that dephosphorylates ^{18}F-FDG-6 phosphate back into ^{18}F-FDG (*4*).

For accurate assessment of the metabolic activity of pathologic tissues (tumor, infection or inflammation, neurogenic and psychogenic brain diseases) and normal tissues, ^{18}F-FDG should be injected when the blood glucose level is ideally within normal limits or near normal (90–100 ± 10 or 20 mg/dL) and the blood insulin level is low. No glucose or insulin should be given during the ^{18}F-FDG uptake period. However, in routine studies, guidelines recommend injection of ^{18}F-FDG when the fasting blood glucose level is at most 150 mg/dL or sometimes even up to 200 mg/dL (*5,6*). Only rarely does ^{18}F-FDG injection proceed despite higher levels of blood glucose (>200 mg/dL); examples of such cases include acute or chronically ill patients and patients with

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poorly controlled diabetes. Rabkin et al. reported that hyperglycemia (>180 mg/dL) does not have a significant effect on the false-negative rate in patients with infection and inflammation (*7*). However, a recent guideline for ^{18}F-FDG PET/CT imaging in large-vessel vasculitis and polymyalgia rheumatica recommends that the study be performed at the lowest possible glucose level, preferably below 126 mg/dL (*8*).

In ^{18}F-FDG PET cardiac viability studies, a blood glucose level of 100–140 mg/dL is recommended at the time of ^{18}F-FDG injection after oral glucose loading when necessary and intravenous insulin administration (*9*).

A high level of blood glucose competes with ^{18}F-FDG and reduces its uptake in pathologic tissues and normal brain. In the presence of a high blood glucose level, the endogenous insulin level also increases, which causes higher ^{18}F-FDG uptake in insulin-sensitive normal tissues (fat and muscle via GLUT4) and a further reduction of ^{18}F-FDG uptake in pathologic tissues and normal brain. As a result, a hyperglycemia-induced decrease in ^{18}F-FDG uptake in pathologic tissues can cause suboptimal differentiation of malignant from benign lesions, underestimation of tumor grade, suboptimal evaluation or overestimation of response to treatment in oncologic cases and infectious or inflammatory diseases, suboptimal evaluation of disease activity in infection and inflammation, false-negative results in patients with fever of unknown origin, and suboptimal results in the brain in dementia patients.

In this study, we analyzed ^{18}F-FDG uptake and activity in the brain, liver, and blood pool at varying blood glucose levels (normoglycemia, hyperglycemia, and hypoglycemia) to understand the effect of blood glucose on ^{18}F-FDG uptake and activity and whether we can develop a formula to correct SUV in hyperglycemic patients.

MATERIALS AND METHODS

In this retrospective study, which was approved by the Kuwait Ministry of Health, whole-body ^{18}F-FDG PET/CT images of adult patients were selected for further analysis. The images were obtained mainly for staging and follow-up of various cancers and in cases of fever of unknown origin or other inflammatory diseases. A Gemini TF PET/CT camera (Philips) was used, with the acquisition occurring 60 min after intravenous injection of 222 MBq (6 mCi) of ^{18}F-FDG. Blood glucose levels were measured using a glucometer before the ^{18}F-FDG was injected. At our institute, we inject ^{18}F-FDG when the blood glucose level is 150 mg/dL or lower. However, in certain cases, we proceed with ^{18}F-FDG injection despite a higher blood glucose level. Before the PET image acquisition, a low-dose CT scan was obtained for attenuation correction and anatomic localization purposes. The PET acquisition was at 3 min/bed position from the top of the head to the mid thighs or the toes. PET images were corrected for attenuation on the basis of the CT data, reconstructed using a standard iterative algorithm, and reformatted into transaxial, coronal, and sagittal views. Maximum-intensity projections were also generated. Both attenuation-corrected and uncorrected PET images, as well as PET/CT fusion images, were reviewed.

We measured SUV in the normal brain (SUV_{max}), liver (SUV_{mean}), and blood pool (SUV_{mean}) at the following glucose ranges (mg/dL): 61–70, 71–80, 81–90, 91–100, 101–110, 111–120, 121–130, 131–140, 141–150, 151–160, 161–170, 171–180, 181–190, 191–200, and 201 and above. At each glucose range, 10 ^{18}F-FDG PET/CT images were analyzed. We excluded images affected by motion artifacts, particularly in the head region, which can cause inaccurate SUVs, and images with intense uptake in large pathologic areas, which can reduce uptake in normal organs, mainly in the brain.

We used SUV_{max} instead SUV_{mean} in the brain. Because of the thin and irregular shape of the cerebral cortex, it is difficult to exclude surrounding low-activity areas (scalp and white matter) from the region of interest (either automated or manually drawn), thus significantly reducing the SUV_{mean}. We used the frontal cortex to measure brain SUV_{max}. SUV_{mean} was more suitable than SUV_{max} for the liver and blood pool (left atrium) because of their homogeneous activity distribution and their larger area and more regular shape—particularly the liver—which enables better placement of the region of interest without including surrounding tissues. If uptake in the left atrial wall obscured the atrial cavity, we used the right atrium, the ventricular cavities, or the aortic cavity for measurement of blood-pool activity. To measure liver activity, the region of interest was placed on the right hepatic lobe away from pathologic regions if present.

The data were managed and statistically analyzed using the Statistical Package for Social Sciences, version 25.0. The mean (±SD) brain SUV_{max}, blood-pool SUV_{mean}, and liver SUV_{mean} at all blood glucose ranges were calculated. These mean values were compared using the nonparametric Mann–Whitney test. A 2-tailed P value of less than 0.05 was considered statistically significant.

We generated SUV and blood glucose curves for the brain, blood pool, and liver. We also generated a formula that can be used to correct SUV in hyperglycemic patients in certain situations. For this formula, to obtain more accurate results, we included 20 studies in the following blood glucose ranges (mg/dL): 81–110 as a reference group, 121–140, 141–160, 161–180, and 181–200. For the blood glucose ranges of 111–120 mg/dL and 201 mg/dL and above, we included 10 studies.

We also applied glucose correction to the measured mean brain SUV_{max} [glucose-corrected SUV = (measured SUV × plasma glucose)/100] for the blood glucose ranges (mg/dL) of 111–120 (mean, 115), 121–140 (mean, 130), 141–160 (mean, 150), 161–180 (mean, 170), 181–200 (mean, 190), and 201 and above and generated a curve to compare with the normal measured mean brain SUV_{max} (*10*).

RESULTS

We analyzed the whole-body ^{18}F-FDG PET/CT images of 150 adults (79 women and 71 men, with a mean age of 58.7 ± 13.7 y and an age range of 23–78 y). Figure 1 shows the curves for mean brain SUV_{max}, blood-pool SUV_{mean}, and liver SUV_{mean} per blood glucose range. Mean brain SUV_{max} gradually reduced with increasing blood glucose level, starting after a level of 110 mg/dL. The mean was 13.78 (considered the normal value) at the reference blood glucose range of 81–110 mg/dL, 11.34 at a range of 111–120 mg/dL (a 17.8% reduction from normal), 8.94 at a range of 121–140 mg/dL (a 35.1% reduction), 6.75 at a range of 141–160 mg/dL (a 51.05% reduction), 5.45 at a range of 161–180 mg/dL (a 60.45% reduction), 5.48 at a range of 181–200

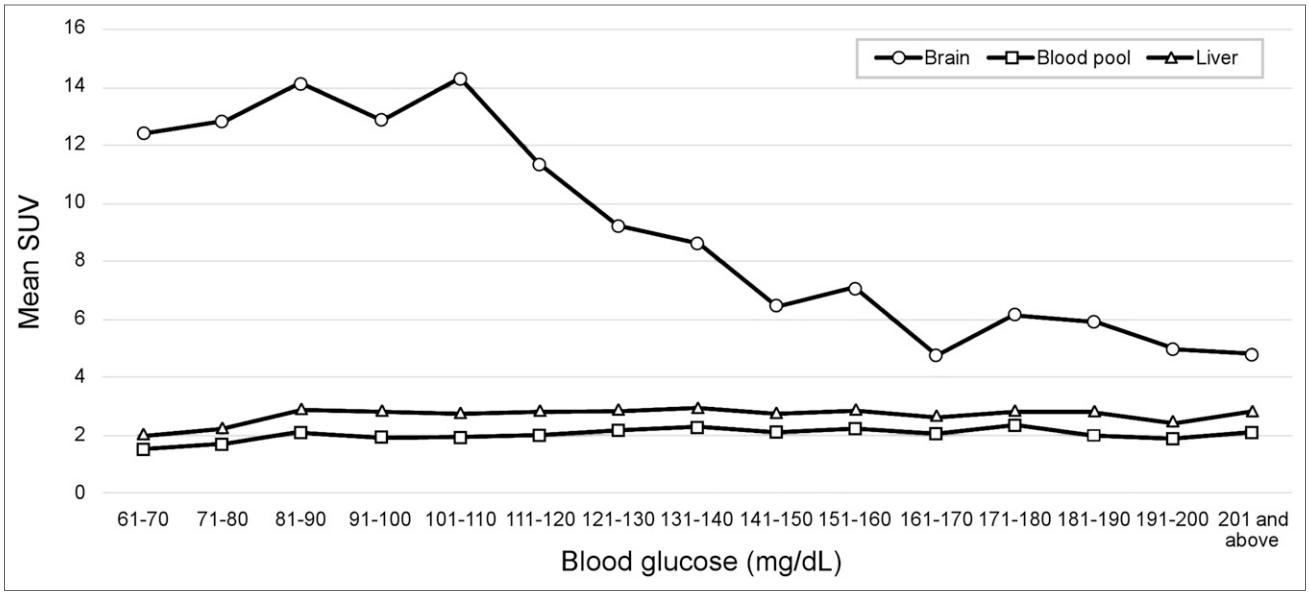

FIGURE 1. SUV and blood glucose curves for brain (SUV_{max}), blood pool (SUV_{mean}), and liver (SUV_{mean}).

mg/dL (a 60.2% reduction), and 4.81 at a range of 201 mg/dL and above (a 65.1% reduction).

We generated a formula for correcting SUV using the percentage reduction in brain SUV_{max} at the various blood glucose ranges:

$$\text{Corrected } SUV_{max} = \text{measured } SUV_{max} \times \text{reduction factor(f)}$$

where

$$f = 100/(100 - \text{percentage reduction in brain } SUV_{max}).$$

Table 1 shows percentage reductions in brain SUV_{max} at various blood glucose ranges and the corresponding reduction factors. In this formula, to calculate corrected SUV, measured SUV_{max} is simply multiplied by the reduction factor for the corresponding blood glucose level seen in Table 1.

As compared with normal values at a blood glucose level of 91–100 mg/dL, statistically there was no significant difference in brain SUV_{max} at blood glucose levels of 61–70 and 71–80 mg/dL ($P > 0.05$).

Figure 2 shows glucose-corrected mean brain SUV_{max} as compared with the measured normal mean brain value (normal, 13.78 at a blood glucose range of 81–110 mg/dL). As seen in this curve, glucose-corrected values are below our normal value, a trend that becomes more prominent with increasing blood glucose levels.

SUV_{mean} in the blood pool was approximately 2 at all blood glucose ranges except 61–70 and 71–80 mg/dL, which were approximately 1.5 (1.54 at 61–70 mg/dL and 1.68 at 71–80 mg/dL). As compared with normal values at a blood glucose level of 91–100 mg/dL, statistically there was a significant difference in SUV_{mean} at a level of 61–70 mg/dL ($P = 0.003$) but no significant difference at 71–80 mg/dL ($P = 0.08$). There was no significant difference in SUV_{mean} between normoglycemic and hyperglycemic patients ($P > 0.05$).

SUV_{mean} in the liver was approximately 3 at all blood glucose ranges, except at 60–71 and 71–80 mg/dL, which were approximately 2 (1.97 at 61–70 mg/dL and 2.25 at 71–80 mg/dL). As compared with normal values at a blood glucose level of 91–100 mg/dL, statistically there was a significant difference in SUV_{mean} at levels of 61–70 mg/dL ($P = 0.0003$) and 71–80 mg/dL ($P = 0.025$). There was no significant difference in liver SUV_{mean} between normoglycemic and hyperglycemic patients ($P > 0.05$).

DISCUSSION

Studies have extensively analyzed the effect of hyperglycemia on ^{18}F-FDG uptake in normal tissues and tumors. It is well known that a high level of blood glucose reduces ^{18}F-FDG uptake in the brain (*11–15*). Hou et al. reported

TABLE 1
Reduction in Brain ^{18}F-FDG Uptake as Compared with Normal Values

Blood glucose (mg/dL)	Approximate reduction (%)	Reduction factor (f)
111–120	20	1.25
121–140	35	1.5
141–160	50	2.0
161–200	60	2.5
≥201	65	2.8

FIGURE 2. Glucose-corrected brain SUV_{max} as compared with measured normal brain SUV_{max} at blood glucose of 81–110 mg/dL.

that chronic hyperglycemia downregulates GLUT1 and GLUT3 expression at both messenger RNA and protein levels in the rat brain (*16*). They suggested that downregulation of GLUT1 and GLUT3 expression might be the adaptive reaction of the body to prevent excessive glucose from entering the cell and potentially leading to cell damage. However, Büsing et al. found that the effect of serum glucose level on tracer uptake in the brain is weaker in diabetic patients than in nondiabetic patients (*12*).

Studies have reported various results for the liver (*12*,*17*–*23*). Although some have reported that hyperglycemia increases ^{18}F-FDG uptake in the liver, some did not find a significant change from normal. Studies have mainly reported that hyperglycemia does not affect blood-pool activity (*12,22,24*), but Malladi et al. found that blood-pool activity differs between normoglycemic and hyperglycemic patients (*18*).

Either unchanged/unaffected or reduced ^{18}F-FDG uptake by tumors has been reported in cases of hyperglycemia (*12,19,20,25*–*32*). The effect of hyperglycemia on tumor ^{18}F-FDG uptake also has varied in different cancer types. Diederichs et al. found a decreased detection rate of pancreatic cancer by ^{18}F-FDG PET in hyperglycemia (*26*). In cervical cancer, there was no hyperglycemia effect on the sensitivity of ^{18}F-FDG PET (*30*). The effect of hyperglycemia on ^{18}F-FDG uptake has also been reported to differ between acute and chronic hyperglycemia. Although many agree that acute hyperglycemia reduces tumor ^{18}F-FDG uptake, there have been different results for chronic hyperglycemia (*12,20,26,30*–*33*). It is believed that chronic hyperglycemia upregulates GLUT1 and GLUT3 in the tumor and is a risk factor in cancer progression (*34*). Hara et al. reported that reduced tumor ^{18}F-FDG uptake is seen mainly in acute hyperglycemia but that chronic hyperglycemia does not have a significant effect on tumor ^{18}F-FDG uptake (*33*). In another study, uptake of ^{18}F-FDG by human adenocarcinoma cells did not significantly change with chronic hyperglycemia, whereas acute hyperglycemia markedly reduced uptake of ^{18}F-FDG (*35*). However, Diederichs and Torizuka et al. reported a reduced ^{18}F-FDG uptake in tumors when diabetes mellitus was present (*26,32*). In chronically hyperglycemic patients, it is still recommended that ^{18}F-FDG be injected when the blood glucose level is within or near normal limits, not high.

In our study, similar to the literature, we found that hyperglycemia reduces ^{18}F-FDG uptake in the brain. Reduction of ^{18}F-FDG uptake in the brain started after a blood glucose level of 110 mg/dL and then became gradually more prominent with increasing blood glucose levels, similar to the literature (*11*). Because there may be a similarity between brain and tumor glucose kinetics, and both brain and tumor show high GLUT1 and GLUT3 expression, and GLUT1 may also be highly expressed in some infections, we generated a formula based on percentage decrease in brain ^{18}F-FDG uptake per blood glucose range that may be used to correct the SUV_{max} of tumoral or infectious lesions when PET images are obtained under hyperglycemic conditions (>110 mg/dL) (*1,36*–*39*). In cases of chronic hyperglycemia, our formula should be used only with caution, since there are no definite results on the effect of chronic hyperglycemia on ^{18}F-FDG uptake in brain and tumors. Our formula appears to be more accurate in cases of acute hyperglycemia than in cases of chronic hyperglycemia.

To better estimate tumor ^{18}F-FDG uptake in patients with hyperglycemia, SUV corrected by blood glucose has been recommended by various studies (*5,10,22,25*). When compared with glucose-corrected SUV, our formula for correcting SUV may be more accurate given the direct assessment of ^{18}F-FDG uptake in the brain at various glucose ranges. As seen in Figure 2, glucose-corrected brain SUVs are lower than our normal measured value, and this trend becomes more prominent with increasing blood glucose levels. This finding may indicate that the blood glucose correction formula underestimates SUV, particularly when the blood glucose level is very high. Although our measured normal brain SUV was not an absolute value, it was near normal.

Our formula should be used carefully because it only approximates the SUV and may not be accurate in certain cases. It should not be used when differentiating benign from malignant lesions, when performing initial staging of the tumor, and when assessing response to treatment in certain cases, because a low or background level of uptake in a lesion could be due to low metabolic activity in the primary lesion or treated disease instead of being the result of hyperglycemia. Our formula may be useful to calculate the metabolic activity of the histopathologically proven primary malignancy if the tumor is well known for ^{18}F-FDG avidity. This consideration is important when comparing

an initial PET scan with a follow-up scan to assess response to nonsurgical treatments such as chemotherapy, radiotherapy, and hormone therapy. In addition, if the follow-up PET scan was taken in a hyperglycemic state for a tumor well known for ^{18}F-FDG avidity, if there is visible uptake in the tumor indicating some residual tumor after treatment, and if the PET findings do not correlate well with the radiologic size of the tumor or tumor markers or with the patient's symptoms and signs, the SUV correction formula might better be used to assess the amount of residual tumor. Such is also true for cases of infection in which the radiologic, laboratory, and clinical findings do not correlate well with the PET findings. If the SUV correction formula is used because of hyperglycemia, such should be noted in the report and both the measured and the corrected SUV should be given in the report, because corrected SUVs are estimates and may not be accurate in some cases. In addition, our formula to correct SUV can be used only in adults, not children, as we assessed only adult images. The SUV in normal and abnormal tissues has been reported to be lower in children than in adults (*40*). ^{18}F-FDG uptake in the normal brain also differs between children and adults (*41*).

SUV is not routinely used in ^{18}F-FDG brain PET studies for dementia cases. Visual assessment and certain semiquantification programs usually help to diagnose or differentiate dementias (*42*). However, because brain ^{18}F-FDG uptake closely relates to blood glucose level, more accurate results can be achieved if ^{18}F-FDG is injected when the blood glucose level is within normal or near-normal limits (90–100 $\pm$ 10 mg/dL). This requirement is important to detect mild regional abnormalities in the brain, visually or semiquantitatively. As seen in our study, reduction in brain ^{18}F-FDG uptake started after a blood glucose level of 110 mg/dL and there was an approximately 20% reduction in normal brain activity at a blood glucose range of 111–120 mg/dL, a trend that became more significant with increasing blood glucose levels. There was at least a 65% reduction from normal when the blood glucose level was 201 mg/dL and above. A hyperglycemia-induced reduction of ^{18}F-FDG uptake in the normal brain may complicate or obscure detection of hypometabolic regions in dementia cases. In addition, high plasma glucose levels have been reported to reduce ^{18}F-FDG uptake in Alzheimer disease–related regions (*43*). ^{18}F-FDG uptake in brain tumors, like the tumors of other systems, is also reduced in hyperglycemia. In the brain, SUV correction by our formula can be used in brain tumors and may also be useful in research studies to correct SUV in healthy control brains.

In our study, there was no difference in brain ^{18}F-FDG uptake between hypoglycemic and normoglycemic patients. Hypoglycemia may activate compensatory mechanisms of glucose metabolism in the brain (*44,45*). Cerebral blood flow and glucose delivery are increased at a plasma glucose level of less than 36 mg/dL in acute hypoglycemia (*45*).

Similar to many previous studies, our study did not find a difference in blood-pool activity between normoglycemic and hyperglycemic patients. The reason is likely attributable to altered tissue distribution and uptake of ^{18}F-FDG in the presence of hyperglycemia, with decreasing uptake in brain and pathologic tissues but increasing uptake in insulin-sensitive tissues such as fat and muscle. In our patients with a blood glucose level of 61–70 mg/dL (hypoglycemia), blood-pool activity was lower, as could be the result of hungry tissues taking up more ^{18}F-FDG than normally and further reducing blood-pool activity.

In our study, ^{18}F-FDG uptake in the liver did not differ between normoglycemic and hyperglycemic patients. Studies reporting higher liver activity in hyperglycemia suggest that increased blood glucose levels lead to increased hepatic glucose uptake, increased glycogen synthesis and storage in the liver, and hence increased ^{18}F-FDG uptake (*20*). The reason we did not find a difference in ^{18}F-FDG uptake between normoglycemic and hyperglycemic patients could be that the rate of glycogen synthesis in the liver is fixed regardless of blood glucose level if there is adequate glycogen storage. In addition, chronic hyperglycemia may downregulate liver GLUTs to protect the liver from hyperglycemia-induced cell damage. Different results for liver SUV in hyperglycemia in various studies could be related to differences in patient populations (age, body mass index, and diabetic status). Groheux et al. reported that ^{18}F-FDG uptake in the liver is affected by patient age and body mass index (*19*). When assessing ^{18}F-FDG uptake in the liver, some studies used SUV_{max} and some used SUV_{mean}, which can also affect the results. We think that SUV_{mean} is more accurate than SUV_{max} for measuring the metabolic activity of the liver because there is a slight heterogeneity in activity distribution in normal liver, with tiny artifactual hot spots (mottled appearance) commonly seen**,** which can create a significant difference in SUV_{max} and SUV_{mean}. The lack of a significant effect of hyperglycemia on ^{18}F-FDG activity in the liver and blood pool in our study and some other studies may indicate that in hyperglycemic patients, liver and blood pool may not be reliable reference areas for assessing tumor metabolic activity in response to treatment.

In our cases with a blood glucose range of 60–80 mg/dL (hypoglycemia and near hypoglycemia), liver uptake was lower than normal, as was also reported by Rosica et al. (*23*). Lower ^{18}F-FDG uptake in the liver in hypoglycemia could be due to reduced glycogen synthesis, as there is glycogen breakdown and release of glucose into the bloodstream.

The brain SUV_{max} of our study was obtained from whole-body PET images (a 3-min acquisition of the brain region with arms up in many patients) and therefore may be lower than SUV_{max} obtained from a standard ^{18}F-FDG brain PET image (a 10- to 15-min acquisition with arms down). However, our brain SUV_{max} results are near normal and adequate to show a percentage decrease in brain uptake with increasing blood glucose level.

CONCLUSION

Hyperglycemia gradually reduces ^{18}F-FDG uptake in the brain, starting after a blood glucose level of 110 mg/dL. Therefore, the ideal blood glucose level for ^{18}F-FDG PET

studies is less than 110 mg/dL. Hyperglycemia does not affect ^{18}F-FDG activity in the liver or blood pool. Therefore, the liver and blood pool may not be reliable reference regions in hyperglycemic patients. Hypoglycemia does not seem to affect ^{18}F-FDG uptake in the brain and appears to reduce liver and blood-pool activity. The simple formula we based on brain SUV_{max} with increasing blood glucose levels can be used to correct the SUV of lesions on ^{18}F-FDG PET studies of hyperglycemic adults in selected cases.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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