Assessing effect of various blood glucose levels on ^{18}F-FDG activity in the brain, liver and blood pool

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ABSTRACT

Objective: Studies have extensively analyzed the effect of hyperglycemia on ^{18}F-fluorodeoxyglucose (^{18}F-FDG or FDG) uptake in normal tissues and tumor. In this study, we measured standardized uptake value (SUV) in the brain, liver and blood pool in normoglycemia, hyperglycemia and hypoglycemia to understand the effect of blood glucose (BG) on FDG uptake and to develop a formula to correct SUV.

Material and Methods: Whole body FDG positron emission tomography/computed tomography (PET/CT) images of adults were selected for analysis. Brain SUVmax, blood pool SUVmean and liver SUVmean were measured for the BG 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. In each BG range, ten (10) PET images were analyzed (total 150). Mean $\pm$ SD of SUV of brain, liver and blood pool in each BG range was calculated and BG/SUV curves were generated. As brain and tumors show high expression of GLUT1 and GLUT3, based on % reduction in brain SUVmax with increasing BG, we generated a formula to correct SUV.

Results: Mean brain SUVmax gradually reduced with increasing BG starting after BG level of 110 mg/dl. Approximate % reduction in brain SUVmax was 20%, 35%, 50%, 60%, and 65% for the BG ranges of 111-120, 121-140, 141-160, 161-200, and $\geq$ 201 mg/dl, respectively. In the formula we generated, measured SUVmax is multiplied by reduction factor of 1.25, 1.5, 2, 2.5 and 2.8 for the BG ranges of 111-120, 121-140 , 141-160 , 161-200 and $\geq$ 201 mg/dl, respectively, to correct SUV. Brain SUVmax was not different in hypoglycemics as compared to normoglycemics (p>0.05). SUVmean in the blood pool and liver were lower in hypoglycemics (p < 0.05) and not different in hyperglycemicss (p>0.05) as compared to normoglycemics.

Conclusion: Hyperglycemia gradually reduces brain FDG uptake starting after BG of 110 mg/dl. Hyperglycemia doesn't affect FDG activity in the liver and blood pool. Hypoglycemia doesn't seem to effect brain 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

INTRODUCTION

Positron emission tomography (PET) imaging with radiolabeled glucose analog, ^{18}F-fluorodeoxyglucose (^{18}F-FDG), is commonly used in oncologic cases and is being increasingly used in neurologic, cardiac and infectious/inflammatory diseases.

Glucose is transported across the plasma membrane into the cytosol by glucose transporters (GLUTs) [1, 2]. There are currently 14 isoforms of the 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 mainly found in insulin-sensitive tissue 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 tricarboxylic acid-TCA cycle or the Krebs 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 which dephosphorylates ^{18}F-FDG-6 phosphate back into ^{18}F-FDG [4].

For accurate assessment of metabolic activity of the pathologic (tumor, infection/inflammation, neurogenic and psychogenic brain diseases) and normal tissues, ^{18}F-FDG should be injected when the blood glucose is ideally within normal limits or near normal (90-100 mg/dl $\pm$ 10 or 20), and blood insulin level is low. No glucose or insulin should be given during uptake period of ^{18}F-FDG.

However, in routine studies, injection of ^{18}F-FDG is recommended when fasting blood glucose level is ≤ 150 mg/dl or even up to 200 mg/dl by guidelines [5, 6]. Rarely, it is proceeded with ^{18}F-FDG injection despite higher levels of blood glucose (>200 mg/dl), particularly in acute and chronically ill patients and poorly controlled diabetics. Rabkin et al. reported that hyperglycemia (>180 mg/dl) does not have significant effect on 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 performing study with the lowest possible glucose level, preferably below 126 mg/dl [8].

In cardiac ^{18}F-FDG PET viability studies, blood glucose level of 100-140 mg/dl is recommended at the time of ^{18}F-FDG injection following oral glucose loading when necessary and intravenous insulin administration [9].

High blood glucose competes with ^{18}F-FDG, and reduces ^{18}F-FDG uptake in pathologic tissues and normal brain. In the presence of high blood glucose, endogenous insulin level also increases which causes higher ^{18}F-FDG uptake in insulin sensitive normal tissues (fat and muscle via GLUT4) and this causes further reduction of ^{18}F-FDG uptake in pathologic tissues and normal brain. As a result, 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/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 cases.

In this study, we analyzed ^{18}F-FDG uptake/activity in the brain, liver and blood pool in varying blood glucose levels (normoglycemia, hyperglycemia and hypoglycemia) to understand effect of

change in blood glucose levels on ^{18}F-FDG uptake/activity in these organs and blood pool and based on these changes if we can develop a formula which can be used to correct standardized uptake value (SUV) in hyperglycemic patients.

MATERIAL AND METHODS

In this retrospective study, whole body ^{18}F-FDG PET/computed tomography (CT) images of adult patients were selected for further analysis. This retrospective study was approved by Kuwait Ministry of Health.

^{18}F-FDG PET/CT images were obtained mainly in various oncologic cases for staging and follow-up of various cancers and also in cases with fever of unknown origin or other inflammatory diseases. PET/CT images were obtained at Philips Gemini Time of Flight PET/CT camera (Philips Medical Systems, Best, Netherlands). PET/CT images were acquired 60 min following intravenous injection of 222 MBq (6 mCi) ^{18}F-FDG. Blood glucose levels were measured using a glucometer before injecting ^{18}F-FDG. At our institute we inject ^{18}F-FDG when the blood glucose is $\leq$ 150 mg/dl. However, in certain cases we proceed with ^{18}F-FDG injection although blood glucose is higher. Prior to PET image acquisition, a low dose CT was obtained for attenuation correction and anatomic localization purposes. PET acquisition was 3 min/bed from top of the head to mid thighs or toes. PET images were corrected for attenuation on the basis of the CT data and reconstructed using a standard iterative algorithm and reformatted into transaxial, coronal and sagittal views. Maximum intensity projection images 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 (SUVmax), liver (SUVmean) and blood pool (SUVmean) for the following glucose ranges as 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. In

each glucose range, ten (10) ^{18}F-FDG PET /CT images were analyzed. Images affected by motion artifacts, particularly in the head region which can cause inaccurate SUV, and images with intense uptake in large pathological large areas which can reduce uptake in normal organs, mainly in the brain, were excluded.

We used SUVmax instead SUVmean in the brain. Because of thin and irregular shape of the cerebral cortex, it is difficult to exclude surrounding low activity areas (scalp and white matter) in the region of interest (ROI) (either automated or manually drawn) which causes significant reduction in SUVmean. We used frontal cortex to measure brain SUVmax. SUVmean was more suitable than SUVmax for the liver and blood pool because of homogenous activity distribution and their larger area and more regular shape, particularly liver, which enables better placing ROI without including surrounding tissues. We used left atrium to measure blood pool activity. In cases with left atrial wall uptake obscuring atrial cavity we used right atrium, ventricular cavities or aortic cavity. To measure liver activity, ROI was placed on right hepatic lobe away from the pathological regions if they were present.

The data management and statistical analysis were carried out using the computer software 'Statistical Package for Social Sciences, SPSS version 25.0'. Mean ± standard deviation (SD) of brain SUVmax, blood pool SUVmean and liver SUVmean were calculated for the all blood glucose ranges. The mean values were compared using non-parametric Mann-Whitney test. The two-tailed probability value 'p' < 0.05 was considered statistically significant.

We generated mean SUV and blood glucose curves for the brain, blood pool and liver. We also generated a formula which can be used to correct SUV in hyperglycemic patients in certain situations as described in the results section. For this formula, to obtain more accurate results, we included 20 studies in following blood glucose ranges as mg/dl (81-110 as normal group, 121-140,

141-160, 161-180, and 181-200). Only in blood glucose ranges of 111-120 mg/dl and 201 mg/dl and above we included 10 studies.

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

RESULTS

Whole body ^{18}F-FDG PET/CT images of 150 adult patients (79 females and 71 males with mean age of 58.7 ± 13.7, ranging from 23 to 78) were analyzed. Figure 1 shows the curves of mean brain SUVmax, blood pool SUVmean and liver SUVmean values per blood glucose ranges. Mean brain SUVmax gradually reduced with increasing blood glucose which started after blood glucose of 110 mg/dl. Mean SUVmax of brain was 13.78 at blood glucose range of 81-110 mg/dl which was considered as normal brain value (including 20 images). Mean SUVmax of brain was 11.34 at blood glucose range of 111-120 mg/dl (17.8% reduction, approximately 20%), 8.94 for blood glucose range of 121-140 mg/dl (35.1 % reduction from normal, approximately 35%), 6.75 for blood glucose range of 141-160 mg/dl (51.05 % reduction from normal, approximately 50%), 5.45 for blood glucose range of 161-180 mg/dl (60.45 % reduction from normal, approximately 60%), 5.48 for blood glucose range of 181-200 mg/dl (60.2 % reduction from normal, approximately 60%) and 4.81 for blood glucose of 201 mg/dl and above (65.1% reduction from normal, approximately 65%).

We generated a formula for correcting SUVs using % reduction in brain SUVmax in various blood glucose ranges:

SUVmax-corrected = SUVmax-measured X reduction factor (f)

f = 100 / (100 - % reduction in brain SUVmax)

Table 1 shows % reductions in brain SUVmax in various blood glucose ranges and corresponding reduction factors (f).

In this formula, to calculate corrected SUV, measured SUVmax is simply multiplied with reduction factor (f) for the corresponding blood glucose level seen in table 1.

As compared with normal values at blood glucose level of 91-100 mg/dl, statistically there was no significant difference in brain SUVmax at blood glucose of 61-70 mg/dl and 71-80 mg/dl (p>0.05).

Figure 2 shows glucose corrected mean brain SUVmax as compared to measured normal mean brain value (normal:13.78 at blood glucose range of 81-110 mg/dl). As seen in this curve glucose corrected values are below our normal value which becomes more prominent with increasing blood glucose levels.

SUVmean in the blood pool was approximately 2 in all blood glucose ranges except in blood glucose levels of 61-70 and 71-80 mg/dl which was approximately 1.5 (1.54 in blood glucose of 61-70 mg/dl, and 1.68 in blood glucose of 71-80 mg/dl). As compared with normal values at blood glucose level of 91-100 mg/dl, statistically there was significant difference in SUVmean at blood glucose of 61-70 mg/dl (p = 0.003) but no significant difference in SUVmean at blood glucose of

71-80 (p= 0.08). There was no significant difference in SUVmean in normoglycemic and hyperglycemic patients (p> 0.05).

SUVmean in the liver was approximately 3 in all blood glucose ranges, except in blood glucose levels of 60-71 and 71-80 mg/dl which was approximately 2 (1.97 in blood glucose 61-70 mg/dl, and 2.25 in blood glucose of 71-80 mg/dl). As compared with normal values at blood glucose level of 91-100 mg/dl, statistically there was significant difference in SUVmean at blood glucose of 61-70 mg/dl (p = 0.0003) and blood glucose of 71-80 mg/dl (p = 0.025). There was no significant difference in liver SUVmean in 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 tumor. It is well known that high blood glucose reduces ^{18}F-FDG uptake in the brain [11-15]. Hou et al. reported that chronic hyperglycemia down-regulates GLUT1 and GLUT3 expression at both mRNA and protein levels in the rat brain [16]. They suggested that down-regulation of GLUT1 and GLUT3 expression might be the adaptive reaction of the body to prevent excessive glucose entering the cell that may lead to cell damage. However, Busing et al. found that in diabetic patients, the effect of serum glucose levels on tracer uptake in the brain is weaker than in non-diabetic patients [12].

Studies have reported various results for the liver. While some reported that hyperglycemia increases ^{18}F-FDG uptake in the liver, some did not find a significant change as compared to normal [17-23]. Studies mainly reported that hyperglycemia does not affect blood pool activity but Malladi et al. reported that blood pool activity show differences in normoglycemic and hyperglycemic patients [12, 18,22, 24].

In tumors, either unchanged/unaffected or reduced ^{18}F-FDG uptake was reported in hyperglycemia [12, 19, 20, 25-32]. The effect of hyperglycemia on tumor ^{18}F-FDG uptake also 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 sensitivity of ^{18}F-FDG PET [30]. The effect of hyperglycemia on ^{18}F-FDG uptake was also reported to be different in acute and chronic hyperglycemia. While many agree that acute hyperglycemia reduces tumor ^{18}F-FDG uptake, there are different results for chronic hyperglycemia [12, 20, 26, 30-33]. It is believed that chronic hyperglycemia up-regulates GLUT1 and GLUT3 in the tumor and it is also a risk factor in cancer progression [34]. Hara et al. reported that reduced tumor ^{18}F-FDG uptake is mainly seen in acute hyperglycemia, but chronic hyperglycemia does not have significant effect on tumor ^{18}F-FDG uptake [33]. Human adeno carcinoma cells did not significantly change ^{18}F-FDG uptake with chronic hyperglycemia while acute hyperglycemia markedly reduced uptake of ^{18}F-FDG [35]. However, Diederisch and Torizuka et al. reported a reduced ^{18}F-FDG uptake in tumors when diabetes mellitus were present [26, 32]. In chronic hyperglycemic patients, it is still recommended injecting ^{18}F-FDG injection when blood glucose level is within normal or near normal limits, not high.

In our study, similar to literature, we found that hyperglycemia reduces ^{18}F-FDG uptake in the brain. Reduction in ^{18}F-FDG uptake in the brain started after blood glucose of 110 mg/dl and then became gradually more prominent with increasing blood glucose levels, similar to literature [11]. Since there may be 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 percent decrease in brain ^{18}F-FDG uptake per blood glucose range which may be used to correct SUVmax of tumoral or infectious lesions when the

PET images were obtained in hyperglycemic conditions (blood glucose > 110 mg/dl) [1, 36-39]. Since there are different and not definite results on effect of chronic hyperglycemia on ^{18}F-FDG uptake in the brain and tumor, our formula may be cautiously used in patients with chronic hyperglycemia. However, in cases with acute hyperglycemia, correcting SUV using our formula appears to be more accurate than using it in chronic hyperglycemia cases.

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

Our formula of correcting SUV, as glucose corrected formula, should be used carefully as they approximately estimate the SUV, and they may even not be accurate in certain cases. They should not be used when differentiating benign from malignant lesions, initial staging of the tumor and assessing response to treatment in certain cases. Because low or background level of uptake in a lesion could be due to low metabolic activity of the primary lesion or treated disease instead of result of hyperglycemia. These formulas may be useful to calculate the metabolic activity of the histopathologically proven primary malignancy if the tumor is well known for its ^{18}F-FDG avidity. This is important when comparing initial PET scan with follow-up scan to assess response to non-surgical treatments such as chemotherapy, radiotherapy, and hormone therapy. In addition, if the follow-up PET scan was taken in hyperglycemic state for a tumor well known for its ^{18}F-FDG

avidity, and there is visible uptake in the tumor indicating some residual tumor after treatment, and PET findings are not well correlating with radiological size of the tumor or tumor markers as well as patient's symptoms/signs, these SUV correction formulas may be used to better assess amount of residual tumor. This is also true for cases with infection with radiological, laboratory and clinical findings which are not well correlating with PET findings. If SUV correction formulas are used due to hyperglycemia, this should be noted in the report and both measured and corrected SUV should be given in the report as corrected SUVs are estimate, not actual, and may even not be accurate in some cases. In addition, our formula to correct SUV, can only be used in adults, not in pediatric cases as we only assessed adult images. In pediatric cases, SUV in normal and abnormal tissues was reported to be lower than adult values [40]. ^{18}F-FDG uptake in the normal brain also shows differences in pediatric cases as compared to 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, as the brain ^{18}F-FDG uptake is closely related to blood glucose level, more accurate results can be achieved if ^{18}F-FDG is injected when blood glucose is within normal or near normal limits (90-100 mg/dl ± 10). This is important to detect mild regional abnormalities in the brain, visually or semiquantitaively. As seen in our study, reduction in brain ^{18}F-FDG uptake started after blood glucose > 110 mg/dl and there was approximately 20% reduction in normal brain activity in blood glucose range of 111-120 mg/dl which became more significant with increasing blood glucose levels and there was at least 65% reduction from normal when blood glucose was 201 mg/dl and above. Hyperglycemia induced reduction of ^{18}F-FDG uptake in the normal brain may complicate/obscure the detection of hypometabolic regions in dementia cases. In addition, it was reported that high plasma glucose levels can reduce ^{18}F-FDG uptake in the Alzheimer's disease

related regions [43]. ^{18}F-FDG uptake in the brain tumors is also reduced in hyperglycemia as in various other system tumors. 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 normal control brains.

In our study there was no difference in brain ^{18}F-FDG uptake in 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 2 mmol/L in acute hypoglycemia [45].

Similar to many previous studies, in our study we did not find a difference in blood pool activity in normoglycemic and hyperglycemic cases. The reason for this is likely due altered tissue distribution/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 cases with blood glucose 61-70 mg/dl (hypoglycemia), blood pool activity was lower which can be result of hungry tissues taking up more ^{18}F-FDG than normal and further reducing blood pool activity.

In our study, ^{18}F-FDG uptake in the liver was not different in normoglycemic and hyperglycemic cases. Studies reporting higher liver activity in hyperglycemia suggest that increased blood glucose levels lead to increased hepatic glucose uptake and glycogen synthesis and storage in the liver and hence increase ^{18}F-FDG uptake [20]. The explanation of our result of not finding a change in ^{18}F-FDG uptake in normoglycemic and with hyperglycemic patients could be due to fixed rate of glycogen synthesis in the liver regardless of blood glucose level if there is adequate glycogen storage. In addition chronic hyperglycemia may down regulate liver GLUTs to protect liver from hyperglycemia induced cell damage. Different results for liver SUV in hyperglycemia in various studies could be related to patient population (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 SUVmax and some used SUVmean which can also affect the results. We think SUVmean is more accurate to measure metabolic activity of the liver than SUVmax as there is slight heterogeneity in activity distribution in normal liver with commonly seen artifactual tiny hot spots (mottled appearance) which can create significant difference in SUVmax and SUVmean. No 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 liver and blood pool may not be reliable reference areas to assess tumor metabolic activity for treatment response assessment in hyperglycemic patients.

In our cases with blood glucose range of 60-80 mg/dl (hypoglycemia and near hypoglycemia), liver uptake was lower than normal which 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 break down and release of glucose into the bloodstream.

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

CONCLUSION

Hyperglycemia gradually reduces brain ^{18}F-FDG uptake in the brain starting after blood glucose of 110 mg/dl. This shows that ideal BG level for ^{18}F-FDG PET studies is less than 110 mg/dl. Hyperglycemia does not affect ^{18}F-FDG activity in the liver and blood pool which may indicate

that liver and blood pool may not be reliable reference regions in hyperglycemic patients. Hypoglycemia does not seem to effect ^{18}F-FDG uptake in the brain. Hypoglycemia appears to reduce liver and blood pool activity. The simple formula we generated based on brain SUVmax with increasing blood glucose levels can be used to correct SUV of lesions on ^{18}F-FDG PET studies in hyperglycemic adults in selected cases.

DISCLOSURE

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

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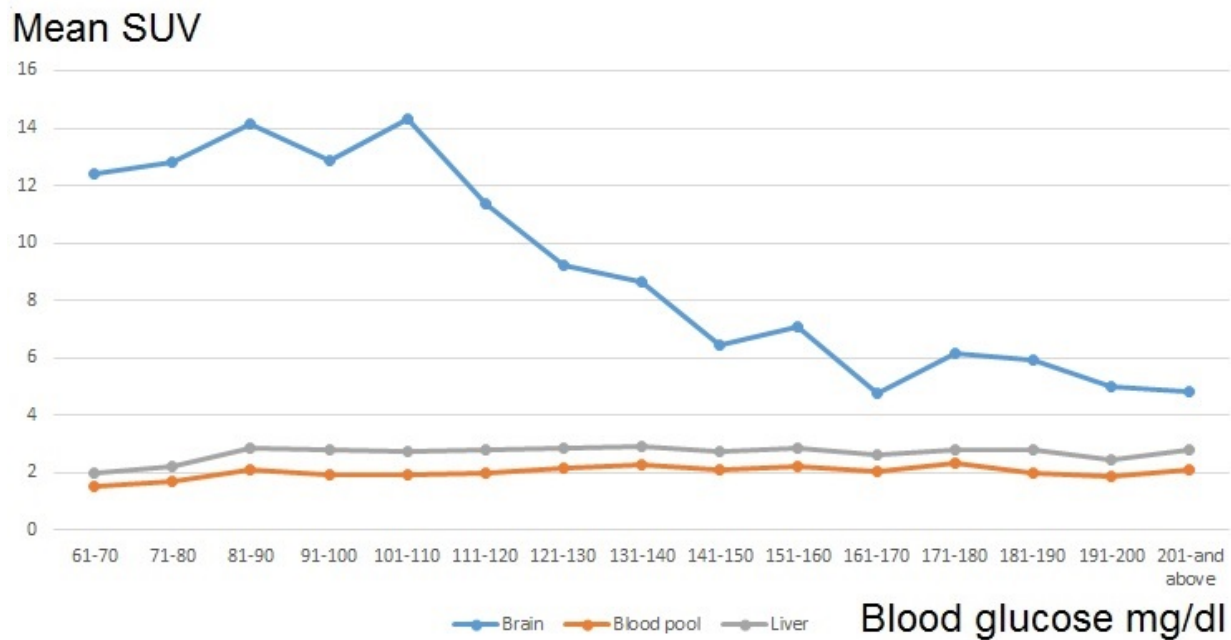
FIGURE LEGENDS

FIGURE 1 Mean SUV and blood glucose curves for brain (SUVmax), blood pool (SUVmean) and liver (SUVmean).
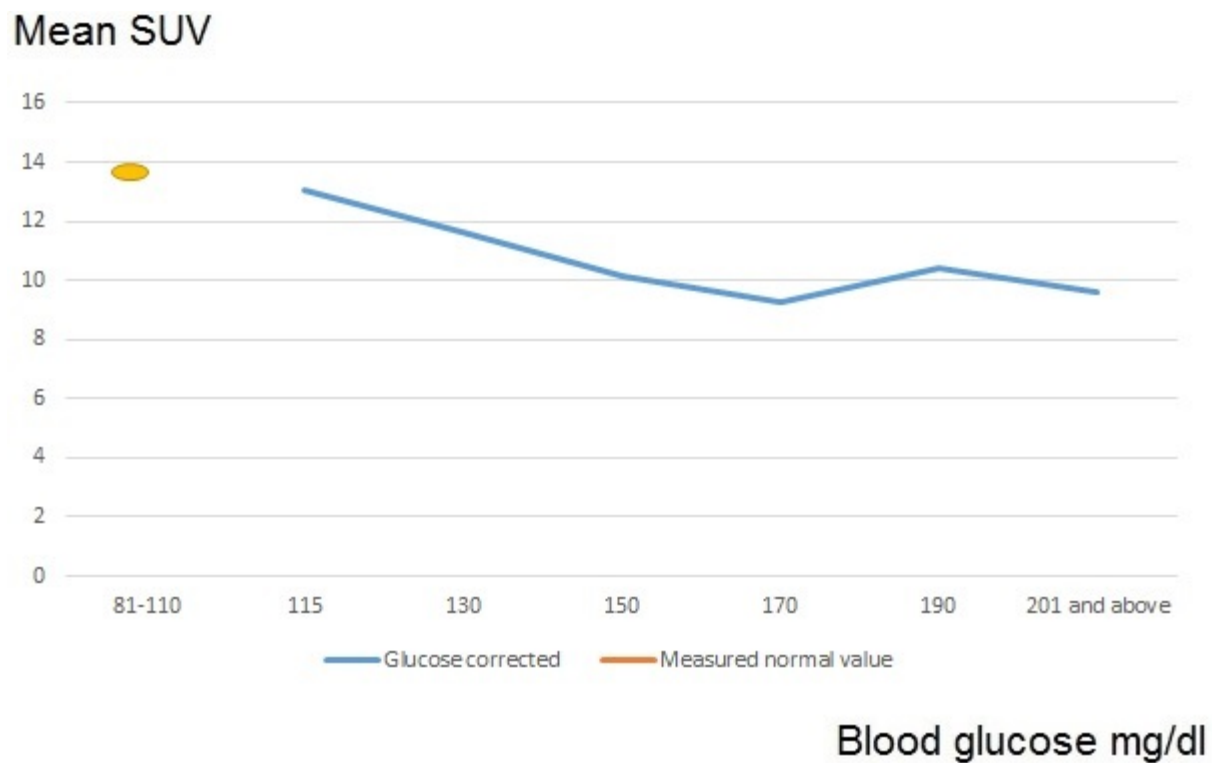
FIGURE 2 Glucose corrected brain SUVmax values as compared to measured normal brain SUVmax at blood glucose of 81-110 mg/dl.

TABLE 1 Approximate % reduction in brain F-18 FDG uptake as compared to normal and f (factor) 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 and above	65	2.8