Review Article, PET/CT.

Does Blood Glucose Level have Influence on ^{18}F-FDG Metabolic Indices in Normal and Neoplastic Tissues?

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ABSTRACT:

In the assessment of the impact of various bloods glucose levels (BGLs) on ^{18}F-FDG uptake values (SUVmax and SUV mean) in normal tissues and neoplastic lesions. There are significant higher SUVmax values among patients with lower BGL in the brain, tonsils as well as in the malignant lesion. In contrary, a significantly higher SUVmax value was found among patients with higher BGL in mediastinal blood pool (MBP), liver, spleen, muscles and bone marrow. Significantly higher SUV mean values were found among patients with lower BGL in the brain. Significantly higher SUV mean values were found among patients with higher BGL in lungs, mediastinal blood pool, liver, spleen, muscles, as well as bone marrow. There was a significant negative correlation between SUVmax and BGL in the brain and tonsils.

A significant positive correlation was existed between SUVmax and BGL in the lungs, MBP, liver, spleen and muscles. DM and obesity also significantly affect SUVs measurements in the brain, bone marrow, lungs, mediastinal blood pool, liver, spleen and muscles. More over IV contrast, diabetes, and obesity had non-significant impact on SUV values calculation in malignant tissues, but on the other hand a significantly higher SUVmax values among patients with blood glucose level 120 – 150 mg/dl (P = 0.02) and significantly lower values in patients who received previous chemotherapy was reported.

Conclusion: Blood glucose levels affect SUV values of both reference organs and neoplastic lesions; therefore nuclear medicine physicians should consider the pre-imaging BGLs in their interpretations of FDG-PET/CT scans.

Key Words: blood glucose level, ^{18}F-FDG, metabolic indices.

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INTRODUCTION:

^{18}F-FDG is the most commonly used radiopharmaceutical for the evaluation of tumor metabolism in PET/CT studies, it could be seen in healthy /normal tissues and tumor tissues, its uptake is frequently adopted as an internal standard reference for degree of tracer accumulation when assessing tumor treatment response in PET studies [(1)]. In clinical practice, ^{18}F-FDG uptake could be analyzed qualitatively by visual comparison of the metabolism in pathological lesions and in normal tissues, or semi-quantitatively using standardized uptake values (SUVs) [(2)]. Standardized uptake values (SUVs), are the most useful widely accepted semi-quantitative metrics used to measure tracer accumulation in tissues in spite of the several sources of bias and variance in their measurements [(2,3)]; especially in the settings of therapy evaluation response and follow-up, however unfortunately they cannot be relied upon exclusively in the diagnostic scans [(4,5)].

^{18}F-FDG uptake and accuracy of SUV measurement can be influence to many technical and biological/patient related factors including sex, age, body mass index, serum creatinine level, blood glucose level (BGL), injected dose, injection-acquisition interval, contrast media, previous therapeutic (e.g. chemotherapy, radiotherapy) and surgical interventions [(7,8)].

Many studies have suggested that various blood glucose levels (BGLs) can influence ^{18}F-FDG uptake in different tissues because of competitive inhibition between labeled and unlabeled glucose and considered a major influence on SUVs values [(9,10)] and that ideally, the ^{18}F-FDG uptake in some tissues such as the liver and mediastinal blood pool, which are commonly used background tissues, should show no variation due to fluctuations in blood glucose level to minimize variability in the assessment of treatment response [(11)].

Sprinz et al, who retrospectively analyzed 5623 patients to see the effects of BGL on ^{18}F-FDG uptake in the liver, lung and brain , found that liver and brain showed significant differences in the average values of SUVmax among different glycemic ranges with the brain being the most affected [(12)], the mechanism is not completely understood; it's postulated that brain behaves in a transporter-limited fashion in the low and normal blood glucose levels, but then switches to an intracellular phosphorylation-limited process in the hyperglycemic state [(13)],

Whereas the lung was the only organ for which correlation of the SUV with glycaemia was not significant, therefore the lung is suggested to be a stable normal background tissue and may serve as an alternative to the liver. ***Sprinz et al,*** also published a systematic review in 2018 to show the effect of various BGLs on ^{18}F-FDG uptake in normal organs **(14)**, they stated that the brain is the only organ in which hyperglycemia has a large effect on the SUV. Although the liver and MBP are significantly impacted by glycaemia, however, they also stated that these effects appear to be too small to be of clinical relevance. They also indicated that the lung, bone marrow, spleen, fat and tumorous lesion were not found to be influenced by the BGLs. Increasing evidence suggests that the spleen harbors stem cells that act as precursors to insulin-producing pancreatic cells **(15)** so it could somehow be influenced by variation in BGL.

Lindholm et al, retrospectively studied 500 patients and they found weak positive correlation between the BGL and the muscle uptake of ^{18}F-FDG since the patients with increased B-glucose are considered to be suffering from chronic hyper-glycaemia **(16)** . It's worth mentioning that most glucose transporters (GLUT) are expressed in a tissue-specific manner. There is a large expression of GLUT4 transporters in skeletal muscles, and thus, it displays increased FDG activity with increased BGL **(17)**.

Lindholm et al, also found that there was no correlation with BGLs and ^{18}F-FDG uptake of the liver, spleen, lungs or bone marrow, and they stated that these organs could be called "indifferent organs" **(16)**.

Regarding effect of diabetes on SUVmax in normal and malignant tissues, the brain (p value< 0.001), tonsils (p value = 0.024), MBP (p value 0.017), fat (p value 0.013), liver (p value 0.013), muscles (p value<0.01) and bone marrow (p value 0.35) are the organs affected by diabetes. Which is in line with the study conducted in 2013 by ***Büsing et al,*** which retrospectively analyzed 900 patients, they also found altered average SUVmax of the brain and muscular tissue in diabetic patients **(6)**, which is most likely attributed to chronic hyperglycemic state that leads to diminished expression of GLUT-4 transporters (down regulated) causing impaired glucose metabolism, and reduced physiological flexibility of glucose uptake. Thus, chronically elevated glucose and insulin levels antagonize the stimulation of GLUT-4 receptor expression in muscular tissue and result in tracer uptake saturation with increasing BGLs.

Regarding the effect of BMI on ^{18}F-FDG uptake, t lungs (p value <0.01), MBP (p value 0.03), liver (p value<0.01), spleen(p value<0.01), muscles(p value<0.01) and bone marrow (p value <0.01) showing significant difference; this is in agreement with a study conducted in 2015 by ***Nordin et al,.*** **(18)** .

Regarding the effect of obesity on semi-quantification of ^{18}F-FDG in the liver in 51 oncology patients, the BMI was significantly affect the physiological ^{18}F-FDG uptake of the liver, this could be explained by the patho-physiological basis of obesity which is associated with an increase in plasma levels of inflammatory cytokines such as tumor necrosis factor alpha (TNF-α) and interleukins-6 (IL-6) **(19)** ; similar cytokines are also secreted by Kupffer cells of the liver **(20)**.

Altered long-term expression of liver metabolic enzymes in obese patients by TNF-α and IL-6 may be critical in the transition to the chronic inflammatory state and subsequently increased FDG avidity **(21)** this might explain strong correlation of physiological liver FDG uptake with BMI in obese patients.

This is in line with the study conducted in 2013 by ***Büsing et al,*** which analyzed ^{18}F-FDG bio-distribution in various organs and documented a statistically significant difference between both groups in almost all organs (including the blood pool) apart from those with a particularly high glucose metabolism (brain, heart) which may be explained by continuous accumulation of considerable amount of ^{18}F-FDG after tracer administration with reduced tracer excretion compared to organs with lesser glucose demand **(5)**.

In analyzing semi quantitative indices of the malignant tissues according to different clinical parameters and blood glucose levels; the IV contrast, diabetes, and obesity had non-significant impact on SUV values calculation but on the other hand, there was significantly higher SUVmax values among patients with blood glucose level 120 – 150 mg/dl (P = 0.02) and significantly lower values in patients who received previous chemotherapy (P = 0.04); That is partially in line with ***Büsing et al,.*** study in 2013, where they concluded that tumoral uptake was not significantly influenced by BGL, diabetes, insulin, obesity or chemotherapy **(6)**.

Regarding the effect of BGL; Another study performed by ***AH Jahromi et al,*** in 2014 studied impact of plasma glucose level at the time of FDG administration on the accuracy of FDG-PET/CT in patients who had pancreatic lesions and concluded that the accuracy of FDG-PET/CT for diagnosis of primary pancreatic lesions is higher in patients with FPG levels < 126 mg/dl than in patients with FPG levels between 126 and 200mg/dl[(22)].

CONCLUSION:

The so-called reference organs i.e. the MBP, liver, spleen, and muscles and malignant lesions are affected with variation in BGLs. Therefore, in light of this: BGLs at the time of imaging should be considered during the process of interpretations of ^{18}F-FDG - PET/CT studies as well as in the follow-up scans. Furthermore, adhering to the guidelines regarding pre-imaging BGLs should be a priority.

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