Original Article, Endocrine.

Association of Standardized Uptake Values in Normal Organs with Serum Blood Glucose in F-18 Fluoro-Deoxy-Glucose Positron Emission Tomography/Computed Tomography in Oncological Patients.

Mostafa, R,.[1] Askar, H,.[2] Helbawi, M,.[2] Mahmoud, H,.[2]

[1]Unit of Nuclear Medicine South Egypt Cancer Institute, [2]Unit of Nuclear Medicine Faculty of Medicine, Assiut University, Egypt.

ABSTRACT:

Objective: To explore the association between SUV max values in normal organs and major influencing factors including serum glucose level. **Materials and methods:** We retrospectively analyzed 523 oncological patients (age range 1-95 years old; 77 patients (14.7%) were diabetic). All patients underwent F 18-FDG PET/CT scans using a routine imaging protocol. Fasting blood glucose at the time of injection, diabetic status, body mass index, uptake period, and injected dose were derived from patients' records. Fixed regions of interest were drawn at healthy organs of interest. The study populations were divided into 2 groups depending on fasting blood glucose levels with a cut-off value of 160 mg/dl. Patients with blood glucose less than 160 mg/dl were considered as a control group. By dividing the difference in the mean SUV max for the group with glucose ≥160 mg/dl by the mean SUV max in the control group, the effect size was calculated using pooled SDs. Multivariate linear regression analysis was used to assess the impact of important factors affecting uptake in normal organs. **Results**: 467 (89.3%) of our study population had fasting blood glucose levels less than 160 mg/dl while 56 had blood glucose ≥ 160. Only *two organs (brain and muscle)* showed a significant association with serum blood glucose (P <0.001, and 0.001 respectively). After adjustment of age, sex, body mass index, injected dose, and serum blood glucose; the *brain* continued to show a significant inverse association with fasting blood glucose (β = -1.86, P <0.001).

Conclusion: The brain was the only organ demonstrating a statistically significant association with serum blood glucose after adjustment for confounding potential values.

Keywords: PET/CT, Blood glucose, normal organs, glycemic state.

Corresponding author: Heba Askar **E-mail: hebaaskar@aun.edu.eg**

INTRODUCTION:

PET/CT using F18- FDG is standardized in clinical practice for diagnosis, staging, and therapeutic response assessment in oncology [1,2]. The FDG molecule acts like glucose and concentrates in most tissues at a rate proportional to glycolysis [2]. The rate and/or overall amount of FDG accumulation in malignant tissues can be determined using a variety of quantitative parameters. The most often utilized parameter is the standardized uptake value (SUV). Several factors can affect its measurement including patient-related factors such as blood glucose level, body mass index, as well as uptake period, injected dose, and inter-scanner variability [3]. SUVs of healthy organs such as liver and mediastinal blood pool activities are considered as references in the evaluation of patients with different tumors such as lymphomas [4]. However, the bio- distribution of FDG in normal tissues and malignancies is complex[5]. Tumors that are highly FDG avid and have heavy tumor loads may change the distribution to normal tissue by preferentially expanding FDG uptake into the cancerous tissue, leaving very little FDG for healthy organs. The effects of technical and patient-related factors on F18- FDG physiological uptake by healthy organs have not been extensively investigated in research. By competing with F18- FDG for glucose transporters (GLUT) and boosting endogenous insulin release, elevated blood glucose level reduces F18- FDG uptake in malignant as well as normal organs [6]. A growing number of patients undergoing PET/CT scans have high blood glucose levels. High blood glucose levels (BGL) in PET-scan patients are commonly caused by diabetes [7], and anxiety [8]. Nutritional imbalances decreased physical activity, old age, obesity, and infection are all contributing factors to the development of hyperglycemia in cancer patients. Furthermore, chemotherapeutic drugs themselves and glucocorticoids used to reduce the side effects of chemotherapy can cause treatment-induced hyperglycemia [9]. PET professionals need to guarantee adequate protocols are in place to avoid non-diagnostic or suboptimal tests, as patient preparation is crucial for obtaining high-quality studies [10]. Various PET scan preparation techniques have attempted to determine the appropriate BGL at the time of scanning, considering the potential impact on FDG uptake and the high prevalence of hyperglycemia. According to the European Association of Nuclear Medicine (EANM), if plasma glucose levels exceed 200 mg/dl, FDG PET/CT studies should be delayed. EANM standards suggest a lower permissible upper pre-scan BGL for research purposes (126-150 mg/dl) [11]. In this study, we aimed to analyze the SUV values of normal organs and assess their association with different factors such as age, sex, uptake period, blood glucose, injected dose, and body mass index.

METHODS and PATEINTS:

Following approval from our institution (Institutional Review Board number. 17300978), we retrospectively assessed 523 patients who acquired F18-FDG PET/CT scans for oncological indications. Written consent was waived. Patients with blood glucose levels

above 200 mg/dL were eliminated from the analysis. Patients' medical records were reviewed to collect clinical and biological demographic data, including age, gender, the primary tumor site, indication for the study, as well as weight, height, diabetic status, diabetic medication (if any), injected F18-FDG dose, and the time interval between FDG injection and imaging.

PET/CT protocol

F18- FDG PET/CT images were done using a standardized clinical protocol according to the European Guidelines for PET/CT imaging [12]. All patients were asked to fast for 6 hours before receiving the F18-FDG injection in order to reduce serum glucose levels and utilization by normal tissues. Serum glucose levels were monitored with a glucometer shortly before FDG administration. After IV injection of a mean dose 7.3±2.7 mCi F18-FDG. During the FDG uptake phase, patients were placed in a warm, quiet environment to reduce undesired FDG uptake. PET/CT images were obtained within a mean of 73.72 minutes following F18-FDG administration utilizing a combined PET/CT scanner. The entire studies were carried out with the arms up, utilizing a three-dimensional (3D) PET/CT system (Biograph m CT Flow, Siemens Healthineers, Erlangen, Germany), which included a PET scanner and a 16-slice CT component. An integrated multi-slice CT system first performs a low-dose CT scan from the skull base to the mid-thigh to adjust for attenuation. Immediately after the low-dose CT, an emission PET scan was acquired in a three-dimensional mode in the cranio- caudal direction over the same anatomical regions starting from the base of the skull to the mid-thighs. The scan duration differed according to body size of the patients. Patients were allowed to breathe normally during imaging. After completion of acquisition, the images are reconstructed with a standard iterative algorithm.

Data reading and imaging analysis

The quantification of 18F-FDG uptake was retrospectively performed. DICOM images were transferred to a Syngo-via viewer. The maximum SUV measurements based on body weight (SUV max) were obtained using the manufacturer's review workstation. Spherical volumes of interest (VOI) were manually positioned over relevant organs using CT images and Syngo-via viewer including right cerebral hemisphere (just lateral to the putamen), right upper lung lobe, mediastinal blood pool activity, right atrium, right lobe of the liver, spleen, pancreas, and muscle. Any organs with infiltrations were excluded.

Statistical analysis

Data was analyzed using Statistical Package for Social Science (SPSS), version 26.0 for Windows. Quantitative data tested for normality by Shapiro-Wilk test data, expressed as mean ± SD according to their normal distribution and qualitative data were expressed as frequencies and percentages. The Independent Sample T-test was used to compare mean difference of SUV max of different organs between the group with glucose < 160 mg/dl Effect size was calculated for each group with glucose ≥160 mg/dl by dividing the difference in the group mean SUV max by the mean SUV max in the control group (glucose <160 mg/dl) using pooled SDs. Pearson correlation was used to explore the correlation between different organs SUV max and other quantitative variables (age, sex, Body Mass Index (BMI), injected dose, and uptake period) before doing multivariate linear regression models. Multivariate Linear regression models were used to investigate whether demographic components and interventional procedures were associated with F18- FDG uptake in normal organs. All final multivariate models were adjusted for age, sex, BMI, activity of injected dose, uptake period, and fasting plasma glucose level. Patients' diabetic status was not included in the model due to correlation and multi collinearity with the independent variable glycemia. The level of significance was considered at P value < 0.05.

RESULTS:

Patient characteristics

Table 1 includes demographic information regarding the study's participants. The table shows 523 patients (282 females and 241 males) with an average age of 46.51 ± 19.67 years. Lymphoma was the most common malignancy in our study sample (235/523), accounting for 44.9%, followed by breast cancer at 13.4%. Only 14.7% of our population had diabetes. 50 individuals had blood glucose levels ≥ 160 mg/dL. The average uptake period was 73.72±20.14 minutes, ranging from 40 to 110 minutes.

Table 1: Demographic information of the study's participants.

	N=523	%
Age (years)		
▪ **< 18 years**	51	9.8%
▪ **≥ 18 years**	472	90.2%
Mean± SD (range)	46.51 ± 19.67 (1-95)	
Gender		
▪ Male	241	46.1%
▪ Female	282	53.9%
Anthropometric measures		
▪ Weight (kg)	70.96±21.21 (7-163)	
▪ Height (cm)	157.78±18.15 (60-195)	
▪ BMI	28.18±8.39 (14.69-129.63)	
Diagnosis		
▪ lymphoma	235	44.9%
▪ breast	70	13.4%
▪ GIT	70	13.4%
▪ others	148	28.3%
Diabetic status		
▪ Diabetic	77	14.7%
▪ Nondiabetic	446	85.3%
Fasting blood glucose		
Mean± SD (range)	112.69±30.05 (54-199)	
▪ < 160 mg/dl	467	89.3%
▪ ≥ 160 mg/dl	56	10.7%
Uptake period	73.72±20.14 (40.0.0-110.0)	

Normal uptake values in the brain and muscles were significantly associated with blood glucose (P-value < 0.001 and 0.001, respectively). Normal uptake values for the lung, blood pool, liver, spleen, and pancreas had no significant association with blood glucose, however the right atrium had a borderline significant association (P = 0.048). Table 2 demonstrates the demographic status of the PET/CT findings according to fasting blood glucose with cut off value 160 mg/dl

Table 2: Demonstrates the demographic status of the PET/CT findings

Parameters	Cut-off value for fasting plasma glucose (mg/dL)		P-value*
	< 160 (n=467)	**≥ 160 (n=56)**	
Age	46.10±19.97	50.11±16.54	0.156
▪ < 18 years	48 (10.3%)	3 (5.4%)	0.241
▪ ≥ 18 years	419 (89.7%)	53 (94.6%)	
Gender			
▪ Male	218 (46.7%)	23 (41.1%)	0.426
▪ Female	249 (53.3%)	33 (58.9%)	
Diabetes mellitus			
▪ Diabetic	**50 (10.7%)**	**27 (48.2%)**	**<0.001**
▪ Nondiabetic	417 (89.3%)	29 (51.8%)	
BMI	**27.93±8.61**	**30.27±5.99**	**0.011**
Injected dose	**7.14±3.88**	**7.78±1.44**	**0.016**
Uptake period	74.01±20.01	71.28±21.20	0.338
PET/CT measurements			
Brain SUV max	**8.67±2.91**	**7.03±2.97**	**<0.001**
▪ Relative difference	-----	-18.9%	
▪ Effect size	-----	0.56	
Lung SUV max	0.72±0.28	0.69±0.22	0.539
▪ Relative difference	-----	-4.2%	
▪ Effect size	-----	0.12	
Blood pool SUV max	1.60±0.51	1.70±0.46	0.192
▪ Relative difference	-----	6.3%	
▪ Effect size	-----	0.20	
Rt atrium SUV max	**1.58±0.56**	**1.74±0.55**	**0.048**
▪ Relative difference	-----	10.1%	
▪ Effect size	-----	0.29	
Liver SUV max	2.29±0.67	2.44±0.64	0.109
▪ Relative difference	-----	6.6%	
▪ Effect size	-----	0.23	
Spleen SUV max	1.91±0.54	2.02±0.49	0.151
▪ Relative difference	-----	5.8%	
▪ Effect size	-----	0.21	
Pancreas SUV max	1.58±0.44	1.59±0.41	0.933
▪ Relative difference	-----	0.6%	
▪ Effect size	-----	0.02	
Muscle SUV max	**0.84±0.30**	**1.02±0.64**	**0.001**
Relative difference	-----	21.4%	
Effect size	-----	0.38	

Figure1 shows the distribution of SUV max values in the brain cortex and skeletal muscle based on serum blood glucose levels. SUV max values of normal organs were corrected for age, gender, BMI, injection dose, uptake time, and blood glucose levels (Table 3). The brain was the only organ showed a statistically significant inverse association with blood glucose (β = -

1.86, P < 0.001) while other organs did not show significant association. Regarding uptake period, the brain showed significant positive association (P = 0.01, β= 0.02) whereas the blood pool, and right atrium demonstrated inverse significant association (P = <0.001, β= -0.004, and -0.01).

Concerning the injected dose and body mass index, all organs showed significant positive association, (β ranged from 0.01 up to 0.12, and P ranged from <0.001 up to 0.02). In respect of age, increasing age did not show significant association with brain SUV max, whilst the blood pool, right atrium, liver, spleen, pancreas, and muscle showed significant positive association with increasing age (β= 0.01, P <0.001), and the lung also demonstrating significant positive association (β=00.2, P =0.01). Regarding sex, female showed significant positive association with brain (β=0.98, P <0.001), lung (β=0.07, P = 0.001), blood pool (β=0.11, P=0.005), liver (β= 0.17, P <0.001), and spleen (β=0.11, P =0.013).

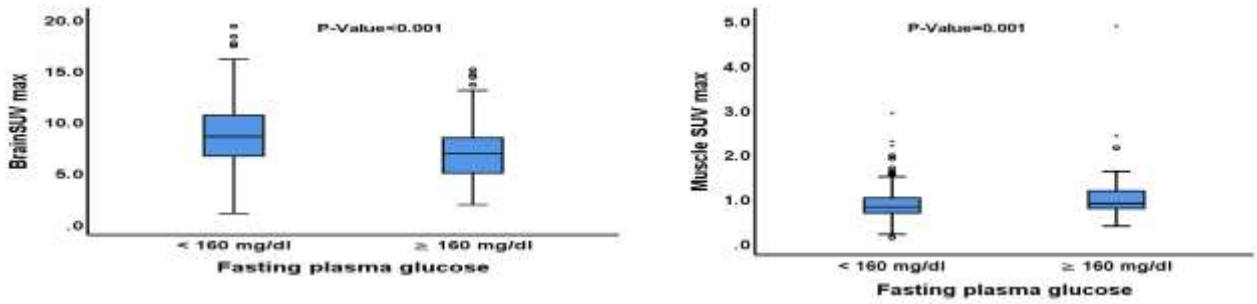

Figure 1: boxplot for distribution of brain and muscle SUV max according to fasting plasma glucose level

DISCUSION:

In this research, we investigated how the level of serum blood glucose correlated with the maximum standardized uptake value (SUV max) shown by healthy organs on F18- FDG PET/CT study. Our findings demonstrated that the brain was the only organs showed significant inverse association with serum blood glucose even after adjustment of otherimportant factors including age, sex, BMI, injected dose, as well as uptake period. A systemicreview published in 2018 totally included 2714 participants; their results demonstrated that the brain was the only notable organ affected by the glycemic status [(4)]. Furthermore, a study conducted by **Sarikaya et al**. 2019 focusing on effect of blood glucose in various brain regions[(13)]. Their results revealed that hyperglycemia induced a significant reduction in various brainregions. Our results agreed with their findings. In our study, we investigated only the cerebralhemisphere uptake which was documented to show the highest F18-FDG uptake. Regarding skeletal muscle uptake in normal and pathological status, a study conducted by **Groves el al** 2004, investigated the physiological causes of increased muscular uptake and thepattern of muscular uptake. Their research described that the pattern of increased uptake in physiological condition usually in a similar appearance unlike pathological conditions that showing asymmetry and

focality [14]. Regarding this fact, we investigated the uptake of the gluteus maximus muscle to represent muscular uptake at our study populations. Our results showed that there is a statistically. significant association with serum blood glucose and muscular uptake. Similar reports described the same finding [15, 16]. Another published study by **Zheng and colleagues** investigated factors that may cause extensive skeletal muscle uptake, their results suggest that fasting time, gastric food residue and proportion of carbohydrate were independent risk factors [17]. Hepatic and mediastinal blood pool activity have been established as reference organs in assessing tumors such as lymphoma, and head and neck tumors [18]. A decade long retrospective study deeply illustrated that age has a greatest impact on the liver and mediastinalblood pool activity [19]. Our results are consistent with their findings; age, sex, and injected dose, showed a positive statistically significant correlation with liver and mediastinal blood pool activity whereas the uptake period showed significant inverse correlation; however, blood glucose levels were not significantly correlated with the hepatic and mediastinal blood pool activities. A study conducted by **Bakker et al** 2019 showed that pancreatic activities among diabetics were significant higher compared to non-diabetics after adjustment of muscle uptake as well as fasting glucose concentration[20]. Our results do not show significant association between pancreatic uptake and serum blood glucose, most probably due to lower number of diabetic patients (77/523). Additionally, we did not include diabetic status in our final multivariate model due to correlation and multi collinearity with the independent variable glycemia.

Finally, we admit several limitations in this work. First, we investigated a diverse group of patients without considering treatment, tumor aggressiveness, tumor type, or age group. Though therapy effects, and types of tumors have a great impact in the uptake of various tissues. However, a future study including specific types of patients with certain inclusion criteria is under investigation. Second, we investigated the maximum SUV values, not the mean, or the peak. Some studies prefer to investigate the mean SUV values not only the maximum SUV values. Nonetheless, indented to mimic the clinical scenario of our daily practice. Third, the retrospective nature of the study with no standardization of the uptake period or injected dose. However, we could mimic our daily practice and investigate those values in our primary and final multivariate mode. On the other hand, our study has some advantages, including reasonable sample size, using same acquisition, reconstruction and processing protocols as well as implementing fixed ROIs.

conclusion, the brain the only two organs demonstrating a statistically significant association with serum blood glucose after adjustment for confounding potential values.

REFERNCES:

1- **Gallamini A, Zwarthoed C, Borra A. et al.** Positron emission tomography (PET) in oncology.Cancers, 6(4): 1821-89; 2014.

2- **Sarji SA.** Physiological uptake in FDG PET simulating disease. Biomedical imaging and intervention journal, 2(4); **2006**.

3- **Adams MC, Turkington TG, Wilson JM, et al.** A systematic review of the factors affecting accuracy of SUV measurements. American Journal of Roentgenology, 195(2): 310- 20; **2010**.

4- **Sprinz C, Altmayer S, Zanon M, et al.** Effects of blood glucose level on 18F-FDG uptake for PET/CT in normal organs: A systematic review. PloS one, 13(2): e0193140; **2018**.

5- **Busing KA, Schonberg SO, Brade J, et al.** Impact of blood glucose, diabetes, insulin,and obesity on standardized uptake values in tumors and healthy organs on 18F-FDG PET/CT. Nucl. Med. Biol. 40(2): 206-13; **2013**.

6- **Finessi M, Bisi G, Deandreis D. et al** Hyperglycemia and 18F-FDG PET/CT, issues andproblem solving: a literature review. Acta diabetologica, 57: 253-62; **2020**.

7- **Cho NH, Shaw JE, Karuranga S, et al.** IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. Diabetes Res Clin Pract, 138: 271-81; **2018**.

8- **Carrasco-Sanchez FJ, Carretero-Gomez J, Gomez-Huelgas R, et al.** Stress-induced hyperglycemia on complications in non-critically elderly hospitalized patients. Rev Clin. Esp. (Barc), 218(5): 223-31; **2018**.

9- **Hwangbo Y and Lee EK.** Acute Hyperglycemia Associated with Anti-Cancer Medication.Endocrinol. Metab. (Seoul), 32(1): 23-9; **2017**.

10- **Hofman MS and Hicks RJ.** How We Read Oncologic FDG PET/CT. Cancer Imaging, 16(1):35; **2016**.

11- **Boellaard R, Delgado-Bolton R, Oyen WJ, et al.** FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0. Eur J Nucl Med Mol Imaging, 42(2): 328-54;**2015**.

12- **Boellaard R, Delgado-Bolton R, Oyen WJ, et al.** FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0. European journal of nuclear medicine and molecular imaging, 42: 328-54; **2015**.

13- **Sarikaya I, Albatineh AN, Sarikayaa A. et al**. Effect of various blood glucose levels on regional FDG uptake in the brain. Asia Oceania Journal of Nuclear Medicine and Biology,8(1): 46; **2020**.

14- **Karunanithi S, Soundararajan R, Sharma P, et al.** Spectrum of physiologic and pathologic skeletal muscle 18F-FDG uptake on PET/CT. American Journal of Roentgenology, 205(2): W141-W9; **2015**.

15- **Lindholm H, Brolin F, Jonsson C, et al.** The relation between the blood glucose leveland the FDG uptake of tissues at normal PET examinations. EJNMMI research, 3(1): 1-5; **2013**.

16- **Cengiz A.** The Relation Between the Blood Glucose Level and the FDG Uptake of Tissues at Normal or Near-Normal PET/CT Imaging. Akdeniz Tıp Dergisi, 5(2): 365-9; **2019**.

17- **Zheng Y, Yuan H, Li Y, et al.** The quantitative carbohydrate ingestion ratio for extensive skeletal muscle uptake in 18F-FDG PET/computed tomography. Nuclear Medicine Communications, 40(9): 927-32; **2019**.

18- **Otomi Y, Arai Y, Otomo M, et al.** Increased physiological [18F] FDG uptake in the liverand blood pool among patients with impaired renal function. Nuclear Medicine Review, 25(2): 95-100; **2022**.

19- **Cao Y, Zhou K, Diao W, et al.** Age-related changes of standardized uptake values in the blood pool and liver: a decade-long retrospective study of the outcomes of 2,526 subjects. Quantitative Imaging in Medicine and Surgery, 11(1): 95; **2021**.

20- **Bakker GJ, Vanbellinghen MC, Scheithauer TP, et al.** Pancreatic 18F-FDG uptake is increased in type 2 diabetes patients compared to non-diabetic controls. Plos one, 14(3): e0213202; **2019**.