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Original

Standardized uptake value of normal organs on routine clinical [18F]FDG PET/CT: impact of tumor metabolism and patient-related factors

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Abstract

Background: To evaluate the effect of patient-related factors such as age, gender, body mass index (BMI), blood glucose (BG), diabetes, serum creatinine and injected dose on ^{18}F-Fluorodeoxyglucose ([^{18}F]FDG) uptake of tumor and normal organs, as well impact of [^{18}F]FDG uptake of tumor on normal organs, in clinical positron emission tomography-computed tomography (PET/CT).

Material and methods: In this retrospective study, data of 200 patients who underwent clinical [^{18}F]FDG PET/CT with (n = 192) and without (n = 8) intravenous contrast was evaluated. Ten target organs and tumor [^{18}F]FDG uptake were measured with a standardized uptake value maximum (SUVmax). Pearson correlation coefficient was calculated for continuous variables while t-test/Wilcoxon rank sum tests were used to compare continuous outcomes. Multivariate linear regression analysis was done to exclude covariates, followed by posthoc multiple linear regression analysis after adjusting the levels of significance.

Results: Significant but weak positive correlation was seen between tumor [18F]FDG uptake with uptake in the pancreas ($r = 0.43$, $p < 0.001$) and heart ($r = 0.19$, $p = 0.049$), but not other organs. With age, a significant negative correlation was seen with the brain ($r = –0.183$, $p = 0.009$) and a positive correlation was seen with the blood pool ($r = 0.205$, $p = 0.003$). With BG, significant negative correlation was seen with the brain ($r = –0.449$, $p < 0.0001$) and heart ($r = –0.15$, $p = 0.033$), while a positive correlation was seen with fat ($r = 0.143$, $p = 0.043$). BMI showed a significant positive correlation with [^{18}F]FDG uptake of all organs except the pancreas and heart, as well as tumor. No significant correlation was seen with serum creatinine and injected [^{18}F]FDG dose. Significantly higher uptake was seen in the brain, spleen, and muscles of females. Between obese and non-obese, a significant difference was seen for all organs except for the pancreas and heart, and tumor. Comparison between non-diabetic and diabetic patients showed significant differences only for bone. Multivariate linear analysis adjusting for cofactors showed only BMI ($p = 0.0009$) and BG ($p = 0.0002$) to be independently correlated with [^{18}F]FDG uptake. Post-hoc multiple regression analysis showed a significant positive correlation between [^{18}F]FDG uptake of the brain ($\beta = 0.118$, $p < 0.001$), liver ($\beta = 0.02$, $p = 0.002$), and fat ($\beta = 0.01$, $p < 0.0006$) with BMI, and significant negative correlation of brain uptake with BG ($\beta = 0.03$, $p < 0.0001$).

Conclusions: Tumor [^{18}F]FDG uptake has no significant effect on the uptake in organs, except for the pancreas and heart. Age, gender, BMI, and BG, but not creatinine and injected [^{18}F]FDG dose show correlation with uptake in tumor and organs. BG and BMI are independent significant factors, with a positive correlation of BMI with the brain, hepatic and fat uptake, and a negative correlation of BG with brain uptake.

KEY words: [^{18}F]FDG; PET/CT; SUV; normal uptake; tumor

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Introduction

Positron emission tomography-computed tomography (PET/CT) with the radiolabeled glucose analog ^{18}F-Fluorodeoxyglucose ([^{18}F]FDG) has revolutionized imaging, especially in the field of oncology. [^{18}F]FDG is taken up by both normal cells utilizing glucose and also the tumor cells which usually have a high glucose demand. This uptake is mediated by the cell surface carrier molecules designated as glucose transporters (GLUT) [1] and can be measured with the semiquantitative index called standardized uptake value (SUV) [2]. The differential [^{18}F]FDG uptake between normal tissue and tumor leads to a high tumor to background contrast, leading to better lesion detection and higher sensitivity. Therefore, apart from the tumor uptake of [^{18}F]FDG, the level of tracer uptake in normal tissue is of crucial importance. Also, relative [^{18}F]FDG uptake of the tumor as compared to normal tissue such as liver, mediastinal blood pool, and muscle is often used to differentiate physiological from pathological uptake, especially in post-therapy setting [3, 4].

The [^{18}F]FDG uptake in tumors as measured with SUV is dependent on various factors [5]. These include the injected [^{18}F]FDG dose and acquisition time after injection. Patient-related factors such as age, gender, body weight, body mass index (BMI), diabetic status, and serum glucose level also influence [^{18}F]FDG uptake. High blood glucose impairs [^{18}F]FDG uptake in both tumor and normal organs by competing with [^{18}F]FDG for GLUT, as well as, by stimulating endogenous insulin secretion leading to stimulated skeletal muscle [^{18}F]FDG uptake [6]. Since [^{18}F]FDG is excreted via the kidneys, deranged renal function can alter its physiological distribution in the body, especially in the blood pool. Also, highly [^{18}F]FDG avid tumors with large tumor burdens can possibly alter tumor to normal tissue distribution with preferential exsanguination into the tumor, leaving very little [^{18}F]FDG for normal organs.

Few studies have evaluated the impact of patient-related factors and tumoral [^{18}F]FDG uptake on physiological [^{18}F]FDG uptake by normal organs, but overall limited studies are available in this regard, most focussing on blood glucose and diabetes [7]. Büsing et al. [8] in their study demonstrated the impact of these factors on the biodistribution of [^{18}F]FDG in muscles and the brain. Also, the impact of renal function on [^{18}F]FDG biodistribution is not properly known, with studies limited to renal failure patients [9]. In addition, it is to be noted that in most of the previous studies the CT part of PET/CT was non-contrast without using any intravenous iodinated contrast, which is now the norm for most clinically acquired PET/CT studies. We have tried to address these issues in the present study and evaluated how patient-related factors and tumoral [^{18}F]FDG uptake influence the SUV of normal organs in routine clinical PET/CT.

Material and methods

The present study was conducted in accordance with the ethical standards of the Helsinki Declaration of 1975, as revised in 2000. However, since there was a retrospective analysis of data, permission from the ethical committee was not required. Written informed consent was obtained from all patients at the time of PET/CT. All identifying information was omitted. Consecutive patients who had undergone whole body [^{18}F]FDG PET/CT for oncological indication were retrospectively included in this study. Patients in whom malignant disease had spread to organs selected for assessing [^{18}F]FDG biodistribution in healthy tissues were excluded from the study population. A total of 200 patients was finally included in the study. Data of these patients was retrieved from the departmental registry and analyzed. The following patient data were retrieved: age (years), gender (male/female), weight (kg), height (m), body mass index [weight in kilograms divided by the square of height in meters (kg/m^2)], serum creatinine (mg/dL), diabetes (present/absent), anti-diabetic medication (if any), blood glucose prior to [^{18}F]FDG injection (BG) and injected [^{18}F]FDG dose [mCi].

Patient preparation

Patient preparation was in accordance with guidelines [10]. All patients fasted for at least 4 hours prior to [^{18}F]FDG injection. Anti-diabetic medications (insulin or oral hypoglycemic agents) if required were taken prior to starting of the fasting period. Parenteral nutrition and intravenous dextrose-containing fluids if any were discontinued 4–6 hours prior to radioisotope injection. Patients were advised to avoid strenuous exercise for at least 6 h before the radioisotope administration, and preferably for 24 h. Blood glucose was measured in all patients prior to [^{18}F]FDG injection. All patients had blood glucose levels below 200 mg/dL as recommended [1]. The patient was then administered [^{18}F]FDG through an intravenous cannula. The administered dose was measured based on a linear relationship formula for PET bed overlap of ≤ 30%, based on EANM guidelines using the formula [FDG activity in MBq for 3D scans = 13.8 × weight/(min/bed) [11]. The actual injected dose was calculated after subtracting pre and post-injection syringe radioactivity. The patient then waited in an adequately warm comfortable room for an uptake prior to 45–60 minutes. None of the patients received oral contrast. They were instructed to drink 1 liter of plain water (if no restriction) during the waiting period which acted as negative oral contrast as well as for hydration.

PET-CT acquisition

Whole body imaging form vortex of the skull to mid-thigh was acquired in all patients with an additional view as and when required. The studies were acquired on a dedicated PET/CT scanner (Discovery 690, GE Healthcare, Waukesha WI, USA). Intravenous iodinated contrast iohexol (1.25 mL/kg with a maximum of 150 mL; Omnipaque 350; GE healthcare, Chicago, Illinois, USA) was administered for the CT part of PET/CT (if no contraindication, depending on estimated glomerular filtration rate). In the PET/CT system, CT acquisition was performed on spiral 16-slice CT with a Kv of 130, mAs of 60, slice thickness of 2 mm, and a pitch of 1. The image was acquired using a matrix of 512 × 512 pixels and a pixel size of 1 mm. After CT, 3D PET acquisition was done for 3 minutes per bed position. PET data was acquired using a matrix of 128 × 128 pixels with a slice thickness of 1.5 mm. CT-based attenuation correction of the emission images was employed. PET images were reconstructed by the iterative method of ordered subset expectation maximization (OSEM; 2 iterations and 8 subsets). After CT acquisition, PET acquisition of the same axial range was done with the patient in the same position. After completion of PET acquisition, the reconstructed attenuation corrected PET images, CT images, and fused images of matching pairs of PET and CT images were available for review in axial, coronal, and

sagittal planes, as well as in maximum intensity projections (MIP) and three-dimensional cine mode.

Image analysis

The PET/CT images were re-evaluated by an experienced nuclear medicine physician (P.S., 13 years of experience in PET/CT). The presence or absence of tumors was noted, and if present the most metabolically active tumor was chosen for semiquantitative analysis. Apart from the tumor ten other healthy organ sites *viz.* brain, lung, heart, liver, spleen, pancreas, bone, muscle, fat, and blood pool were also semiquantitatively evaluated. The semiquantitative analysis was done using the maximum standardized uptake value (SUVmax). The SUV calculation was done via the default method by body weight [(SUV = mean ROI activity (MBq/g)/injected activity (MBq)/body weight (g)]. For measurement of SUVmax of tumor, multiple circular ROIs were drawn covering the tumor over its entire length. For healthy organs, a circular ROI of 10 mm diameter was drawn [brain: left sensorimotor cortex; lung: right lung lower lobe superior segment; heart: lateral wall of left ventricle; liver: right lobe segment 8; spleen: central part; pancreas: body; bone: body of L2 vertebra; muscle: right erector spinae; fat: upper back and blood pool: descending thoracic aorta].

Statistical analysis

Quantitative data were described using mean, standard deviation (SD), median, and range while categorical data were described using frequency and proportion. Pearson correlation coefficients (r) were calculated among continuous variables. Unpaired t-test or Satterthwaite corrected t-test were used to compare the Gaussian continuous outcomes according to binary categorical variables while non-parametric Wilcoxon rank sum test was used for non-Gaussian outcomes. Since the multiple outcomes were correlated, therefore, we used a multivariate linear regression analysis to assess the effects of different patient factors on outcomes after adjusting other cofactors followed by posthoc multiple linear regression analysis after adjusting the levels of significance. Hotelling-Lawley Trace p-values were reported in multivariate analysis. In the posthoc linear regression analysis, we considered the level of significance at 0.01 while a 5% level of significance was considered in univariate analysis. All the statistical analyses were carried out using Statistical Analysis System 9.3 (SAS Institute Inc., Cary, North Carolina, USA).

Results

Patient details are presented in Table 1. Of the 46 diabetic patients, 38 were on oral hypoglycemic agents while 8 were on insulin. Total of 11/200 patients had elevated serum creatinine (> 1.3 mg/dL), of which two were on dialysis. 126 patients had received either radiotherapy or chemotherapy or a combination therapy prior to PET/CT. The rest of them were treatment-naive patients. Eight patients (5 for renal derangement, 3 for prior severe contrast reaction) underwent non-contrast PET/CT, while the remaining 192 patients received intravenous contrast.

[^{18}F]FDG uptake values of tumors and organs are detailed in Table 2. On the assessment of the correlation of tumor [^{18}F]FDG uptake with other organs (Fig. 1), a significant positive correlation was seen between tumor uptake with the pancreas (r = 0.43, p < 0.001) and just significant positive correlation was seen with the heart (r = 0.19, p = 0.049). The [18F]FDG uptake of other sites, including liver (r = 0.46, p = 0.63) and blood pool (r= 0.117, p = 0.229) was not significant, either positively or negatively, correlated with tumor uptake. The results of the correlation analysis between [18F]FDG uptake and different patient parameters are presented

Table 1. Patient demographics and clinical profile

Parameter	Mean ± SD	Range
Age [years]	55.1 ± 15.0	6–86
BMI [kg/m^2]	24.0 ± 5.3	13–60
Creatinine [mg/dL]	0.9 ± 0.4	0.3–4.4
Blood glucose [mg/dL]	119.1 ± 22.7	59–194
Injected [^{18}F]FDG dose [mCi]	11.3 ± 1.4	6–15
Parameter	**Number (%)**	
Gender		
Male	109 (54.5%)	
Female	91 (45.5%)	
Diabetes		
Absent	154 (77%)	
Present	46 (23%)	
Obesity (BMI ≥ 25)		
Yes	117 (58.5%)	
No	83 (41.5%)	
Indication		
Lung cancer	37 (18.5%)	
Breast cancer	32 (16.0%)	
Lymphoma	41 (20.5%)	
Head and neck cancer	25 (12.5%)	
Esophageal cancer	12 (6%)	
Colorectal cancer	15 (7.5%)	
Hepatobiliary cancer	9 (4.5%)	
Renal cancer	7 (3.5%)	
Urinary bladder cancer	2 (1%)	
Gynaecological cancer	16 (8%)	
Others	4 (2%)	

SD — standard deviation; BMI — body mass index

Table 2. Standardized uptake value maximum (SUVmax) of tumor and organs

SUVmax	Mean ± SD	Range
Tumor	5.1 ± 2.9	0.9–19.8
Brain	5.9 ± 1.6	2.1–13.5
Lung	0.6 ± 0.5	0.2–5.2
Heart	3.1 ± 2.3	0.7–10.4
Liver	1.6 ± 0.5	0.8–3.9
Spleen	1.3 ± 0.3	0.6–3.3
Pancreas	1.0 ± 0.5	0.4–8.5
Bone	1.2 ± 0.5	0.6–5.5
Muscle	0.6 ± 0.2	0.3–2.9
Fat	0.6 ± 0.2	0.3–1.7
Blood pool	1.0 ± 0.3	0.6–4

SD — standard deviation

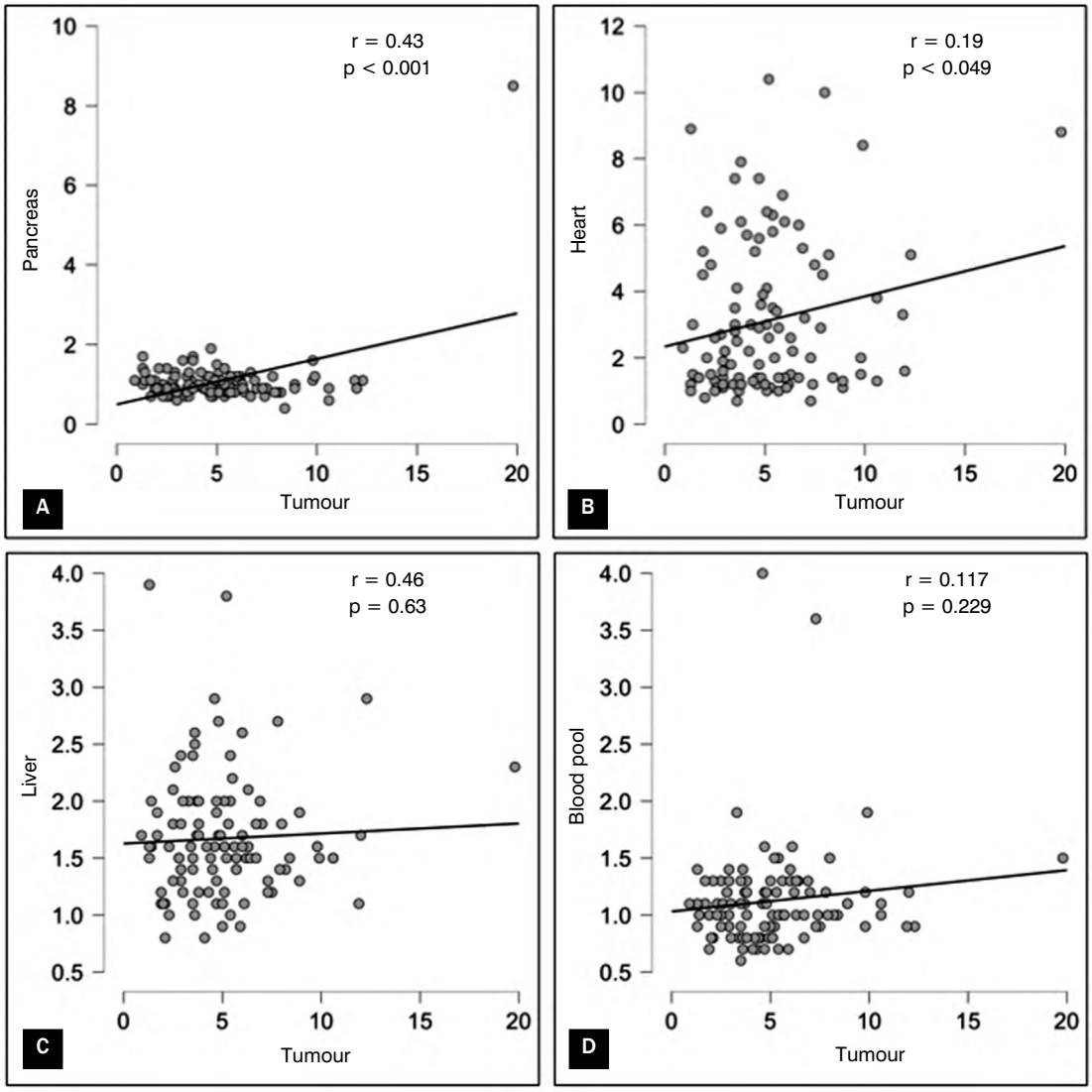

Figure 1. Scatter plots showing a correlation between SUVmax of a tumor with SUVmax of the pancreas (**A**), heart (**B**), liver (**C**), and blood pool (**D**). The correlation was significant and positive for the pancreas and heart, while no correlation was seen for the liver and blood pool (p-value < 0.05 was significant)

in Table 3 (Fig. 2). A significant negative correlation was found between [^{18}F]FDG uptake of the brain with age, while a positive correlation was seen between age and blood pool [^{18}F]FDG uptake. A significant negative correlation was seen between [^{18}F]FDG uptake of brain and heart with BG, while a significant positive correlation was seen with [^{18}F]FDG uptake of fat and BG. BMI showed a significant positive correlation with [^{18}F]FDG uptake of all organs except the pancreas and heart, apart from the tumor. No significant correlation was seen between [^{18}F]FDG uptake of tumor and organs with serum creatinine level and injected [^{18}F]FDG dose. On comparing [^{18}F]FDG uptake in tumors and different organs among male and female patients, significantly higher SUVmax was seen in the brain, spleen, and muscles of females (Tab. 4). On comparing [^{18}F]FDG uptake in tumors and different organs among obese and non-obese patients, a significant difference was seen for all organs except for the pancreas, heart, and tumor (Tab. 5). A comparison of [^{18}F]FDG uptake between non-diabetic and diabetic patients showed a significant difference only for bone (Tab. 6).

Multivariate linear analysis after adjusting for cofactors showed a significant association of [^{18}F]FDG uptake with BMI and BG but not age, gender, and creatinine (Tab. 7). Post hoc multiple regression analysis (Tab. 8, Fig. 3) after adjusting for the level of significance, showed a significant positive association of [^{18}F]FDG uptake of the brain with BMI and a significant negative association with BG. A significant positive association was seen between [^{18}F]FDG uptake of liver and fat with BMI.

Discussion

[^{18}F]FDG PET/CT is now an integral part of the management of a wide array of cancers, with use including but not limited to diagnosis, staging, response evaluation, restaging, and prognostication. SUVmax of the tumor is an important semi-quantitative parameter used for differentiating benign from malignant lesions, with the latter usually showing high values. More significantly, SUVmax is used for the assessment of response to anti-cancer

Table 3. Correlation between [^{18}F]FDG uptake (SUVmax) of tumor and organs with age, BMI, creatinine, BG, and injected dose

SUVmax	Age r (p-value)	BMI r (p-value)	Creatinine r (p-value)	BG r (p-value)	Injected dose r (p-value)
Tumor	0.021 (0.825)	0.021 (0.825)	−0.043 (0.656)	−0.011 (0.906)	−0.107 (0.271)
Brain	−0.183 (0.009*)	0.394 (<.0001*)	−0.117 (0.098)	−0.449 (< 0.0001*)	0.032 (0.643)
Lung	0.032 (0.643)	0.112 (0.0012*)	−0.037 (0.597)	−0.009 (0.896)	0.024 (0.727)
Heart	0.056 (0.426)	−0.051 (0.465)	0.023 (0.738)	−0.15 (0.033*)	−0.02 (0.774)
Liver	0.092 (0.193)	0.267 (0.0001*)	−0.072 (0.304)	−0.052 (0.458)	0.021 (0.765)
Spleen	0.075 (0.29)	0.367 (< 0.0001*)	−0.029 (0.675)	0.108 (0.126)	0.099 (0.159)
Pancreas	−0.085 (0.229)	−0.041 (0.558)	−0.044 (0.527)	−0.03 (0.665)	−0.043 (0.539)
Bone	−0.027 (0.703)	0.23 (0.001*)	0.113 (0.109)	0.067 (0.345)	0.003 (0.96)
Muscle	0.055 (0.438)	0.203 (0.003*)	−0.072 (0.31)	0.125 (0.075)	0.095 (0.178)
Fat	0.137 (0.052)	0.352 (< 0.0001*)	−0.002 (0.966)	0.143 (0.043*)	−0.025 (0.724)
Blood pool	0.205 (0.003*)	0.251 (0.0003*)	−0.125 (0.077)	0.072 (0.308)	−0.028 (0.688)

*p-value < 0.05; BG — blood glucose; BMI — body mass index; r — pearson's correlation coefficient; SUVmax — standardized uptake value maximum

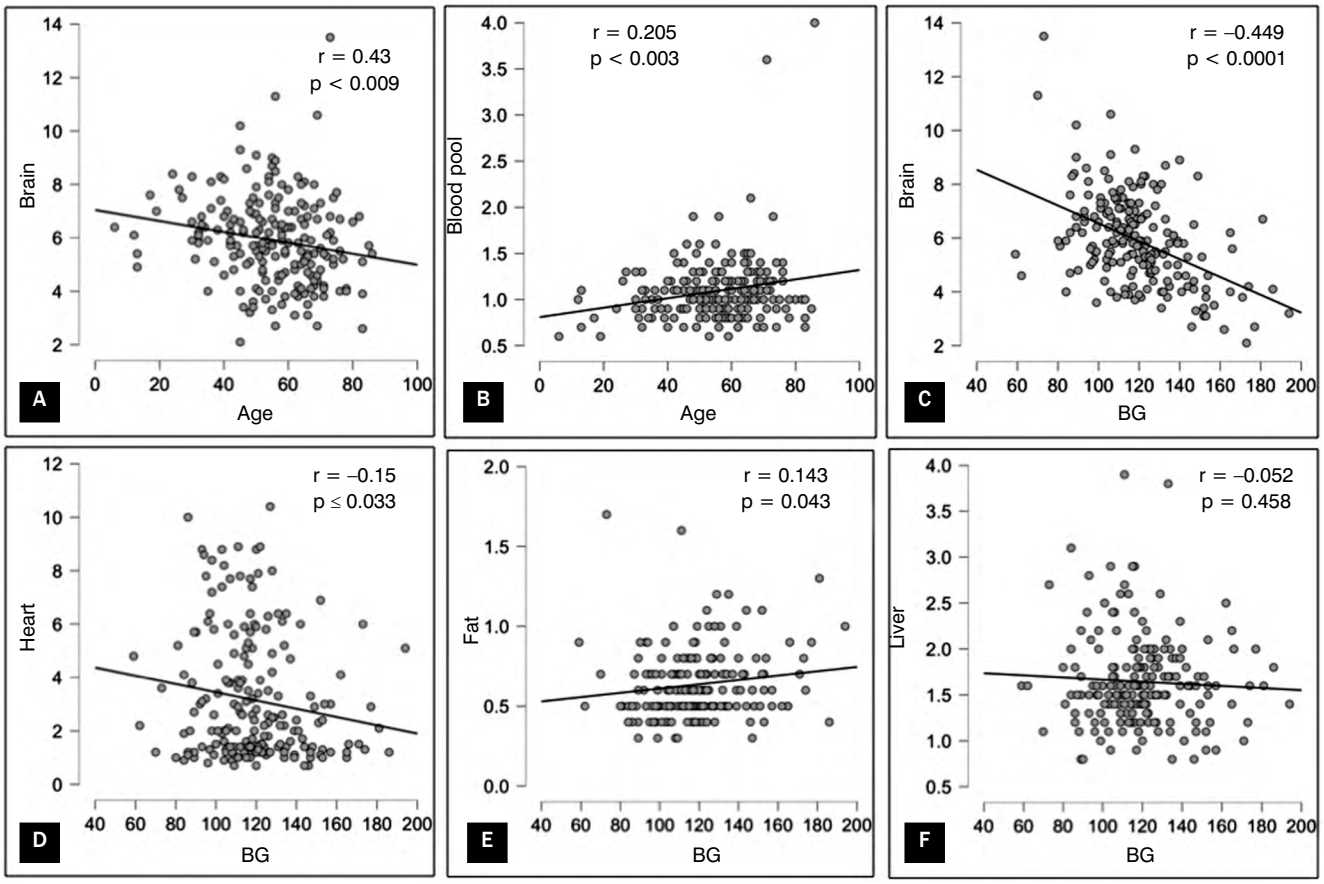

Figure 2. Scatter plots showing a correlation between SUVmax of different organs with patient-related factors. For age, a significant negative correlation was seen with the brain (**A**) and a significant positive correlation was seen with the blood pool (**B**). For blood glucose, a significant negative correlation was seen with the brain (**C**), a significant positive correlation was seen for the heart (**D**) and fat (**E**), and no significant correlation was seen for the liver (**F**) (p-value < 0.05 was significant); BG — blood glucose

Table 4. [18F]FDG uptake (SUVmax) comparison based on gender

	SUVmax (Mean ± SD)		
Site	Male	Female	p-value
Tumor	5.10 ± 2.67	5.12 ± 3.21	0.974
Brain	5.61 ± 1.63	6.26 ± 5.91	0.005#
Lung*	0.69 ± 0.59	0.69 ± 0.41	0.410
Heart*	3.19 ± 2.25	3.09 ± 2.45	0.546
Liver	1.66 ± 0.53	1.62 ± 0.44	0.619
Spleen	1.27 ± 0.364	1.4 ± 0.33	0.01#
Pancreas	0.96 ± 0.26	1.10 ± 0.81	0.123
Bone	1.21 ± 0.58	1.31 ± 0.58	0.251
Muscle	0.61 ± 0.21	0.72 ± 0.3	0.007#
Fat	0.61 ± 0.22	0.66 ± 0.2	0.149
Blood pool	1.05 ± 0.44	1.13 ± 0.26	0.09

*Wilcoxon rank sum test; #p-value is significant (< 0.05); SUVmax — standardized uptake value maximum

Table 5. [18]FDG uptake (SUVmax) comparison based on BMI stratification

	SUV max (Mean ± SD)		
Site	Non-obese (BMI < 25)	Obese (BMI ≥ 25)	p-value
Tumor	5.03 ± 3.24	5.24 ± 2.23	0.705
Brain	5.34 ± 1.39	6.71 ± 1.73	< 0.0001#
Lung*	0.64 ± 0.57	0.76 ± 0.41	< 0.0001#
Heart*	3.19 ± 2.4	3.08 ± 2.25	0.550
Liver	1.56 ± 0.51	1.75 ± 0.45	0.006#
Spleen	1.24 ± 0.33	1.45 ± 0.345	< 0.0001#
Pancreas	1.04 ± 0.74	1.00 ± 0.24	0.584
Bone	1.16 ± 0.58	1.38 ± 0.55	0.009#
Muscle	0.63 ± 0.27	0.70 ± 0.23	0.053
Fat	0.58 ± 0.205	0.70 ± 0.21	0.0002#
Blood pool	1.02 ± 0.36	1.17 ± 0.374	0.005#

*Wilcoxon rank sum test; #p-value is significant (< 0.05); BMI — body mass index; SD — standard deviation; SUVmax — standardized uptake value maximum

Table 6. [18F]FDG uptake (SUVmax) comparison based on diabetes

	SUVmax (Mean ± SD)		
Site	Non-diabetic	Diabetic	p-value
Tumor	5.05 ± 2.94	5.35 ± 2.73	0.67
Brain	5.93 ± 1.56	5.83 ± 2.04	0.769
Lung*	0.7 ± 0.61	0.66 ± 0.32	0.767
Heart*	3.29 ± 2.45	2.65 ± 1.83	0.218
Liver	1.64 ± 0.51	1.65 ± 0.44	0.837
Spleen	1.32 ± 0.36	1.35 ± 0.31	0.532
Pancreas	1.04 ± 0.65	0.97 ± 0.26	0.269
Bone	1.3 ± 0.63	1.11 ± 0.33	0.009#
Muscle	0.67 ± 0.27	0.65 ± 0.19	0.628
Fat	0.629 ± 0.19	0.65 ± 0.27	0.507
Blood pool	1.08 ± 0.35	1.1 ± 0.43	0.86

*Wilcoxon rank sum test; #p-value is significant (< 0.05); SUVmax — standardized uptake value maximum

Table 7. Multivariate association analysis of cofactors with [^{18}F]FDG uptake of organs and tumor

Variables	p-value
BMI	0.0009*
Creatinine	0.432
Blood Glucose (BG)	0.0002*
Age	0.347
Gender	0.526

*Hotelling-Lawley trace p-value < 0.05; BMI — body mass index

treatment, comparing pre-treatment with post-treatment values. However, since SUV values are affected by many factors and can vary from center to center because of different acquisition systems, for some settings visual scoring systems have been suggested. This includes visually comparing [^{18}F]FDG uptake in a tumor with that of a normal structure as well as numerical uptake ratios [12]. Deauville score for high-grade lymphoma [3] and Hopkin's score for head and neck cancers [4] are two such examples, with robust validations. This brings forward the issue of [^{18}F]FDG uptake in normal structures/organs which are the denominators for such scores. It is therefore relevant to know how the tumor metabolism and patient-related factors impact [^{18}F]FDG uptake in normal organs. We have tried to evaluate the same in the present study.

On the assessment of the impact of tumor [^{18}F]FDG uptake on other organs, we found a significant positive correlation only with the pancreas and just about a significant positive correlation with the heart. The [^{18}F]FDG uptake of other sites was not significantly, either positively or negatively, correlated with tumor uptake. This implies that high [^{18}F]FDG uptake of tumor does not significantly affect uptake in other organs, especially the liver and blood pool, which are widely employed for response categorization. So, the scary-looking visualization of tumor only PET/CT scans is more a function of normalization. However, this interpretation is with two caveats. Firstly, we excluded patients with widely disseminated disease, so that organ SUV values can be measured without interference. This meant the tumor burden in our study was small to medium. Secondly, the mean tumor SUVmax values in our study were high but not very high.

On the evaluation of the impact of age, we found that among the organs evaluated only SUVmax of brain and blood pool showed a significant correlation with changing age. The SUV of the brain was negatively correlated with age, suggesting a significant reduction with age. This could be because of aging-related neuronal loss [13]. Other factors which might be responsible are the higher prevalence of diabetes with increasing age as well as impaired glucose metabolic capabilities of the aging brain over and above neuronal loss. We also found that blood pool SUVmax significantly increased with age. Impaired overall utilization of [^{18}F]FDG by various organs, increased [^{18}F]FDG uptake in the aging aortic wall with partial volume averaging [14] and increasing prevalence of diabetes in the elderly population could account for this finding. When evaluating the impact of BG, we found its significant negative correlation with [^{18}F]FDG uptake of the brain and heart. In the case of the brain, this could be a result of diminished expression of GLUT-4 transporter, impaired glucose metabolism,

Table 8. Results of post-hoc linear regression analysis

SUVmax	Age ß (p-value)	BMI ß (p-value)	Creatinine ß (p-value)	BG ß (p-value)	Gender ß (p-value)
Tumor	0.005 (0.804)	0.01 (0.829)	−0.25 (0.677)	−0.0002 (0.986)	−0.072 (0.908)
Brain	−0.007 (0.485)	0.118 (< 0.001*)	0.002 (0.993)	−0.03 (< 0.0001*)	0.15 (0.601)
Lung	−0.002 (0.661)	0.005 (0.61)	−0.109 (0.432)	−0.0004 (0.863)	−0.045 (0.748)
Heart	0.003 (0.845)	−0.04 (0.321)	0.387 (0.421)	−0.014 (0.115)	−0.292 (0.552)
Liver	0.00002 (0.99)	0.02 (0.002*)	−0.16 (0.138)	0.0004 (0.85)	−0.19 (0.085)
Spleen	−0.003 (0.302)	0.014 (0.038)	−0.02 (0.744)	0.001 (0.286)	0.078 (0.348)
Pancreas	−0.01 (0.081)	−0.01 (0.161)	−0.07 (0.648)	−0.0004 (0.881)	0.196 (0.232)
Bone	−0.004 (0.376)	0.019 (0.134)	0.256 (0.09)	0.001 (0.523)	0.035 (0.818)
Muscle	0.0004 (0.828)	0.01 (0.045)	−0.01 (0.808)	0.0008 (0.464)	0.089 (0.16)
Fat	0.002 (0.234)	0.01 (0.006*)	0.02 (0.544)	0.0005 (0.547)	0.02 (0.589)
Blood pool	0.006 (0.078)	0.014 (0.063)	−0.17 (0.061)	0.001 (0.488)	−0.06 (0.464)

*p-value < 0.01; SUVmax — standardized uptake value maximum; BMI — body mass index; BG — blood glucose; ß — regression coefficient

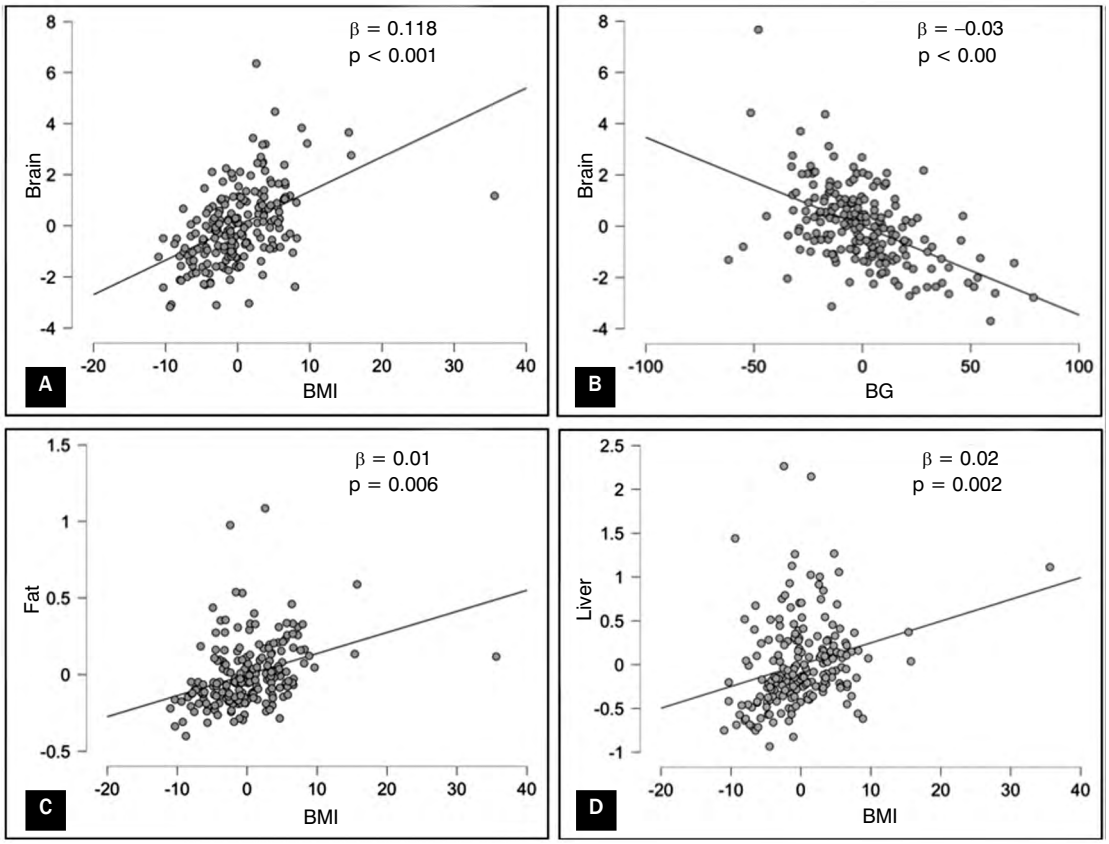

Figure 3. Scatter plots showing results of posthoc regression analysis for independently correlated patient factors. A significant positive correlation was found between brain SUVmax and body mass index (**A**), while a significant negative correlation was found with blood glucose (**B**). A significant positive correlation was also seen between BMI with fat (**C**) and liver (**D**) SUVmax. No significant correlation was seen between other sites and tumors (p-value < 0.01 was significant); BG — blood glucose; BMI — body mass index

and reduced physiological flexibility in chronic hyperglycemia [15]. The same factors can be true for the heart. But a more important reason could be the "metabolic switch" from glucose to fatty acid seen in normal myocardium in fasting states with low BG levels. This finding is similar to that reported by Kaneta et al. [16]. Israel et al. [17] on the other hand reported the opposite finding, but their study population had hyperglycemia and diabetes that could have brought the outcome. We also found a significant positive correlation between [^{18}F]FDG uptake of fat and BG, probably because of the fact that glucose metabolism in white adipose tissue is regulated by insulin-mediated GLUT-4 [18], therefore higher BG with resultant insulin response will lead to an elevated SUV in adipose tissue. Also, adipose tissue inflammation associated with metabolic syndrome could be a reason for this positive correlation [19].

BMI showed a significant positive correlation with [^{18}F]FDG uptake of all organs except the pancreas and heart, as well as tumors. When comparing [^{18}F]FDG uptake among obese and non-obese patients, we found significantly higher SUVmax for all organs in obese group except for the pancreas, heart, and tumor. This could be because of the impact of body weight on SUV values, which has been shown to result in overestimation in an obese patient, both for normal organs and tumors [20]. In fact, to eliminate the confounding impact of body weight, SUV values normalized to lean body mass (SUL) have been recommended by some authors [21]. No significant correlation was seen between [^{18}F]FDG uptake of tumor and organs with serum creatinine level and injected [^{18}F]FDG dose. We didn't compare the values between those with normal and raised serum creatinine, as the number in the latter group was very small. A similar comparison by Büsing et al. also didn't find any significant difference [8].

When evaluating the impact of gender on SUVmax of normal organs, we found significantly higher SUVmax in the brain, spleen, and muscles of females, but not for other sites. Many factors could account for this finding including differing glucose metabolism between sexes [22], women having more body fat and lower lean body mass for the same weight [23], and a more active immune system in women [24].

An important finding of the present study was no significant difference in [^{18}F]FDG uptake of tumors and other organs between non-diabetic and diabetic patients, except for bone, where it was higher for non-diabetics. This implies that in patients with well or moderately controlled diabetes with BG ≤ 200 mg/dL at the time of [^{18}F]FDG injection and sufficient interval after antidiabetic medications, the presence of diabetes alone is not an important factor in determining SUVmax values [1]. In fact, as mentioned earlier, it is the pre-injection BG that impacts SUV values of many organs, not the presence or absence of diabetes *per se*. Many

previous studies including that by Büsing et al. [8] have shown that organs, especially the brain and tumor uptake are impaired in diabetics, while muscle and myocardial uptake is increased. However, that could have been because of the fact that many patients in those study groups had higher BG and received insulin to bring it down. High BG leads to competition with the glucose analog [^{8}F]FDG, relocation of GLUT-4 from cell membranes to the cytosol and stimulates the release of insulin which promotes [^{18}F]FDG migration to muscles, including myocardium [25, 26].

Since some of the variables we evaluated were interrelated such as age and diabetic status, gender and BMI, age and BG, etc., we performed a multivariate analysis to look for independent variables impacting [^{18}F]FDG uptake. On multivariate linear analysis after adjusting for cofactors, a significant association of SUVmax (tumor and organ) was seen with BMI and BG but not age, gender, and creatinine. Also on posthoc multiple regression analysis for tumor and organ SUVmax after adjusting for the level of significance, [^{18}F]FDG uptake of the brain showed a significant positive association with BMI and a significant negative association with BG. This is in keeping with previously published studies. A significant positive association was also seen between [^{18}F]FDG uptake of liver and fat with BMI but not with BG. These findings highlight the fact that a rising BMI can lead to high SUVmax values of brain, liver, and fat independent of age, gender and creatinine level therefore a better standardization technique such as using lean body mass might possibly be better. Also, in patients with BG within accepted limits (≤ 200 mg/dL), there is no significant impact of BG on organ and tumor SUV, except for the brain, where higher BG is associated with poorer [^{18}F]FDG uptake. Therefore, better BG control is more stringently needed for patients undergoing [^{18}F]FDG PET/CT for brain pathologies. Also, since hepatic and blood pool uptake are not significantly associated with these factors, scoring systems using them should continue to be useful, with attention towards liver uptake in patients with high BMI.

Our study is not without limitations. Firstly, this was a retrospective analysis with all its associated shortcomings. Secondly, because of the limited number of patients with renal impairment we were not able to compare the SUV values between those with and without renal impairment. Finally, we didn't have a biochemical proof for many of our hypotheses such as insulin level, tumoral and organ GLUT-4 expression, and markers for inflammation, thus reducing the validity of our arguments. Larger multicentre studies addressing these shortcomings are warranted in the future.

Conclusions

In clinical PET-CT imaging, the level of tumoral [^{18}F]FDG uptake has no significant negative effect on the uptake in organs and has a weak positive correlation with uptake in the pancreas and heart. Only age, gender, BMI, and BG, not creatinine, and injected [^{18}F]FDG dose show positive or negative correlation with uptake in tumor and few other organs, with only BG and BMI being independent significant factors. BMI has a significant positive correlation with brain, hepatic and fat uptake, while brain [^{18}F]FDG uptake was negatively correlated with BG. No independent correlation was seen for other sites and factors.

References

1. Pauwels EK, Ribeiro MJ, Stoot JH, et al. FDG accumulation and tumor biology. Nucl Med Biol. 1998; 25(4): 317–322, doi: 10.1016/s0969-8051(97)00226-6, indexed in Pubmed: 9639291.
2. Sollini M, Bandera F, Kirienko M. Quantitative imaging biomarkers in nuclear medicine: from SUV to image mining studies. Highlights from annals of nuclear medicine 2018. Eur J Nucl Med Mol Imaging. 2019; 46(13): 2737–2745, doi: 10.1007/s00259-019-04531-0, indexed in Pubmed: 31690962.
3. Bakhshi S, Bhethanabhotla S, Kumar R, et al. Posttreatment PET/CT rather than interim PET/CT using deauville criteria predicts outcome in pediatric hodgkin lymphoma: a prospective study comparing PET/CT with conventional imaging. J Nucl Med. 2017; 58(4): 577–583, doi: 10.2967/jnumed.116.176511, indexed in Pubmed: 27754902.
4. Marcus C, Ciarallo A, Tahari AK, et al. Head and neck PET/CT: therapy response interpretation criteria (Hopkins Criteria)-interreader reliability, accuracy, and survival outcomes. J Nucl Med. 2014; 55(9): 1411–1416, doi: 10.2967/jnumed.113.136796, indexed in Pubmed: 24947059.
5. Lodge MA. Repeatability of SUV in Oncologic F-FDG PET. J Nucl Med. 2017; 58(4): 523–532, doi: 10.2967/jnumed.116.186353, indexed in Pubmed: 28232605.
6. Chen YC, Wang QQ, Wang YH, et al. Intravenous regular insulin is an efficient and safe procedure for obtaining high-quality cardiac F-FDG PET images: an open-label, single-center, randomized controlled prospective trial. J Nucl Cardiol. 2022; 29(1): 239–247, doi: 10.1007/s12350-020-02219-9, indexed in Pubmed: 32533427.
7. 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. 2018; 13(2): e0193140, doi: 10.1371/journal.pone.0193140, indexed in Pubmed: 29486008.
8. Büsing KA, Schönberg 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. 2013; 40(2): 206–213, doi: 10.1016/j.nucmedbio.2012.10.014, indexed in Pubmed: 23228852.
9. Minamimoto R, Takahashi N, Inoue T. FDG-PET of patients with suspected renal failure: standardized uptake values in normal tissues. Ann Nucl Med. 2007; 21(4): 217–222, doi: 10.1007/s12149-007-0012-4, indexed in Pubmed: 17581720.
10. Boellaard R, Delgado-Bolton R, Oyen WJG, et al. FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0. Eur J Nucl Med Mol Imaging. 2015; 42(2): 328–354, doi: 10.1007/s00259-014-2961-x, indexed in Pubmed: 25452219.
11. de Groot EH, Post N, Boellaard R, et al. Optimized dose regimen for whole-body FDG-PET imaging. EJNMMI Res. 2013; 3(1): 63, doi: 10.1186/2191-219X-3-63, indexed in Pubmed: 23938036.
12. Santra A, Kumar R, Sharma P, et al. F-18 FDG PET-CT for predicting survival in patients with recurrent glioma: a prospective study. Neuroradiology. 2011; 53(12): 1017–1024, doi: 10.1007/s00234-011-0898-3, indexed in Pubmed: 21739222.
13. Pourhassan Shamchi S, Khosravi M, Taghvaei R, et al. Normal patterns of regional brain F-FDG uptake in normal aging. Hell J Nucl Med. 2018; 21(3): 175–180, doi: 10.1967/s002449910902, indexed in Pubmed: 30411727.
14. Bural GG, Torigian DA, Chamroonrat W, et al. FDG-PET is an effective imaging modality to detect and quantify age-related atherosclerosis in large arteries. Eur J Nucl Med Mol Imaging. 2008; 35(3): 562–569, doi: 10.1007/s00259-007-0528-9, indexed in Pubmed: 17957367.
15. Slieker LJ, Sundell KL, Heath WF, et al. Glucose transporter levels in tissues of spontaneously diabetic Zucker fa/fa rat (ZDF/drt) and viable yellow mouse (Avy/a). Diabetes. 1992; 41(2): 187–193, doi: 10.2337/diab.41.2.187, indexed in Pubmed: 1733808.
16. Kaneta T, Hakamatsuka T, Takanami K, et al. Evaluation of the relationship between physiological FDG uptake in the heart and age, blood glucose level,

fasting period, and hospitalization. Ann Nucl Med. 2006; 20(3): 203–208, doi: 10.1007/BF03027431, indexed in Pubmed: 16715951.

17. Israel O, Weiler-Sagie M, Rispler S, et al. PET/CT quantitation of the effect of patient-related factors on cardiac 18F-FDG uptake. J Nucl Med. 2007; 48(2): 234–239, indexed in Pubmed: 17268020.
18. Rosen ED, Spiegelman BM. Adipocytes as regulators of energy balance and glucose homeostasis. Nature. 2006; 444(7121): 847–853, doi: 10.1038/nature05483, indexed in Pubmed: 17167472.
19. Pahk K, Kim EJu, Lee YJ, et al. Characterization of glucose uptake metabolism in visceral fat by 18 F-FDG PET/CT reflects inflammatory status in metabolic syndrome. PLoS One. 2020; 15(2): e0228602, doi: 10.1371/journal.pone.0228602, indexed in Pubmed: 32027706.
20. Sarikaya I, Albatineh AN, Sarikaya A. Revisiting weight-normalized SUV and lean-body-mass-normalized SUV in PET studies. J Nucl Med Technol. 2020; 48(2): 163–167, doi: 10.2967/jnmt.119.233353, indexed in Pubmed: 31604893.
21. Tahari AK, Chien D, Azadi JR, et al. Optimum lean body formulation for correction of standardized uptake value in PET imaging. J Nucl Med. 2014; 55(9): 1481–1484, doi: 10.2967/jnumed.113.136986, indexed in Pubmed: 24963129.
22. Blaak E. Sex differences in the control of glucose homeostasis. Curr Opin Clin Nutr Metab Care. 2008; 11(4): 500–504, doi: 10.1097/MCO.0b013e32830467d3, indexed in Pubmed: 18542013.
23. Deurenberg P, Weststrate JA, Seidell JC. Body mass index as a measure of body fatness: age- and sex-specific prediction formulas. Br J Nutr. 1991; 65(2): 105–114, doi: 10.1079/bjn19910073, indexed in Pubmed: 2043597.
24. Klein SL, Flanagan KL. Sex differences in immune responses. Nat Rev Immunol. 2016; 16(10): 626–638, doi: 10.1038/nri.2016.90, indexed in Pubmed: 27546235.
25. Zhao S, Kuge Y, Tsukamoto E, et al. Effects of insulin and glucose loading on FDG uptake in experimental malignant tumours and inflammatory lesions. Eur J Nucl Med. 2001; 28(6): 730–735, doi: 10.1007/s002590100517, indexed in Pubmed: 11440033.
26. Shepherd PR, Kahn BB. Glucose transporters and insulin action--implications for insulin resistance and diabetes mellitus. N Engl J Med. 1999; 341(4): 248–257, doi: 10.1056/NEJM199907223410406, indexed in Pubmed: 10413738.