The influence of adipose tissue volume can significantly affect the metabolic activity of reference organs in ^{18}F-FDG PET/CT studies of a normal healthy population

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Abstract

Objective: This study investigated whether fluorine-18-fluorodeoxyglucose (^{18}F-FDG) uptake of reference organs can be affected by subjects' factors in positron emission tomography/computed tomography (PET/CT) in a healthy population. **Subjects and Methods:** A total of 208 normal healthy subjects without diabetes or dyslipidemia were included. Adipose tissue volume was measured by CT images from a dedicated PET/CT scan. Uptake of ^{18}F-FDG of reference organs was measured from liver, blood pool, and muscle, and was normalized by lean body anthropometric data and adipose tissue volume. **Results:** Of 208 participants, 118 were metabolically healthy lean (MHL); with body mass index (BMI) <25kg/m^2 and 90 were metabolically healthy obese (MHO) with; BMI ≥25kg/m^2. These subjects had significantly higher values of liver, blood pool, and muscle than did the MHL subjects (P<0.001 for both). Among subjects' factors, adipose tis-sue volume revealed strongest correlation with standardized uptake value multiplied by lean body weight divided by body weight (SUL) of liver (r=0.754, P<0.001), of blood pool (r=0.756, P<0.001) and of muscle (r= 0.635, P<0.001). On regression analysis, adipose tissue volume was determined to be a common independent predictor for SUL of liver, blood pool and muscle (P<0.001) and furthermore was serum C-reactive protein level for SUL of the liver and also age and serum insulin level for SUL of blood pool. **Conclusion:** Adipose tissue volume can significantly affect SUL of liver, blood pool, and muscle in a healthy population. Liver and blood pool may have limited roles as reference organs for normalization of ^{18}F-FDG uptake of the lesion.

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Introduction

Currently, fluorine-18-fluorodeoxyglocose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT), that can detect glucose metabolism of tissues, has been widely used in diagnosis, staging and restaging of various kinds of cancer [1]. In clinical conditions, ^{18}F-FDG PET/CT images are routinely analyzed using standardized uptake value (SUV) for semi-quantification of ^{18}F-FDG uptake of malignant lesions [2-4]. Standardized uptake value is influenced by several factors relative to patients such as body mass and serum glucose level as well as PET/CT factors. Therefore, the need to normalize methods of SUV has been advocated to reduce the variability of SUV between patients and between initial and follow-up PET/CT images of the same patient.

As SUV of liver and mediastinal blood pool have been shown in a previous study to be stable over time [5]. Most clinical studies with ^{18}F-FDG PET/CT have used liver or mediastinal blood pool as reference organs to normalize ^{18}F-FDG uptake of tumors to be used in SUV [6-8].

Several previous studies using tumor-to-liver uptake ratio or tumor-to-blood pool uptake ratio validated that those values were significantly associated with clinical outcomes and had more accurate prognostic value than SUV [6, 9-12]. However, other more recent studies reported that the liver may not be suitable as a reference organ, due to fluctuation of liver to blood uptake ratio and of serum glucose level [13, 14]. Besides, another study revealed that ^{18}F-FDG uptake of blood pool on PET/CT may be affected by several factors such as metabolism of vessel wall and atherosclerosis [15]. Therefore, more extensive studies are needed relative to using liver and blood pool as reference organs.

In this study, we measured SUV of liver, blood pool, and muscle, which are candidates for reference organs, normalized by lean body mass, in 208 normal healthy subjects without diabetes or dyslipidemia and also studied whether ^{18}F-FDG uptake of these organs can be affected by the clinical condition of subjects and mainly by adipose tissues.

Subjects and Methods

A total of 208 normal healthy subjects that had a screening medical checkup at our health promotion center from March 2015 to February 2016 were retrospectively enrolled (written informed consent was obtained from all subjects for the nuclear medicine tests). All subjects had a ^{18}F-FDG PET/CT scan and serological testing including complete blood counts, liver enzymes, cholesterol profile, glucose, glycated hemoglobin, insulin, and C-reactive protein (CRP) on the same day. Exclusion criteria were: subjects that had: (a) a history of major abdominal surgery, (b) diabetes or dyslipidemia, (c) positive serum hepatitis viral marker, (d) fatty liver disease on ultrasonographic findings, (e) active systemic infectious or inflammatory disease, (f) inappropriate CT scan for analyzing fat measurement due to presence of gross beam-hardening artifact, or (g) activated brown fat tissue on ^{18}F-FDG PET/CT [16]. Height and body weight of subjects were measured before the ^{18}F-FDG PET/CT scan. Body mass index (BMI) was calculated as body weight (kg) divided by the square of height (m).

Blood samples were collected in the morning after overnight fasting. Plasma glucose, total cholesterol, triglyceride (TG), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl transferase (γ-GT), CRP, insulin, and glycated hemoglobin (HbA-1C) were measured.

This retrospective study was approved by the Institutional Review Board of Soonchunhayng University Cheonan Hospital (2017-06-040).

^{18}F-FDG PET/CT

All subjects fasted for at least eight hours before intravenous injection of ^{18}F-FDG. Blood glucose level was checked to ensure it was <200mg/dL before the injection. PET/CT images were acquired from skull to proximal thigh using a dedicated scanner (Biograph mCT 128; Siemens Healthcare, Knoxville, TN, USA) one hour after injection of 4.07MBq/kg of ^{18}F-FDG. Initially, CT scan for attenuation correction was conducted without contrast-enhancement (using a standard protocol: 80mAs, 120kVp with automated dose modulation, axial field of view 780mm, slice thickness 5mm, slice increment 2.5 mm), followed by emission scan with 1.5 minute per bed position. Images from PET were reconstructed using ordered-subset expectation maximization algorithm with time-of-flight mode with attenuation correction (2 iterations, 21 subsets).

PET/CT image analysis

Positron emission tomography/CT images were retrospectively assessed by CT images using a U.S. Food and Drug Administration-approved DICOM viewer, Osirix MD software (Pixmeo, Switzerland) according to the method used in our previous study [16]. At first, adipose tissue volume was measured on three consecutive slices at the level of L4/L5 intervertebral space. The areas with Hounsfield unit from -190 to -30 on CT images were automatically computed as adipose tissue in cm3 (Figure 1).

The SUV of reference organs was obtained from liver, blood pool and muscle for each patient. Mean SUV of liver defined as an average value of three regions of interest (ROI) drawn in right hepatic lobe. Mean SUV of blood pool was obtained by drawing ROI in the aortic arch. Mean SUV of muscle was obtained by drawing ROI in the vastus lateralis muscle (Figure 2).

Afterwards, SUV of liver, blood pool, and muscle for each patient were normalized by lean body mass (SUL). Standardized uptake values were used to correct body weight dependency of SUV because SUV may be affected by body weight [17]. Lean body mass (LBM) for each patient was calculated as follows: LBM (for males)=48.0+1.06×(height-152), LBM (for females)=45.5+0.91×(height-152) [18]. SUL was calculated by multiplying SUV by the LBM divided by body weight.

Statistical analyses

Student t-test, Mann-Whitney U test and chi-square test were used to compares variables between metabolically healthy obese (MHO) and metabolically healthy lean (MHL) groups. Correlations between mean SUL (liver, blood pool, and muscle) and serologic tests and between mean SUL and adipose tissue volume were evaluated with the Pearson coefficient. Linear regression analysis and multiple stepwise linear regression analysis were used to determine independent factors affecting mean SUL of liver, blood pool, and muscle. Statistical analyses were performed using Medcalc version 17.5.3 (MedCalc Software bvba, Ostend, Belgium). A P-value <0.05 was considered significant.

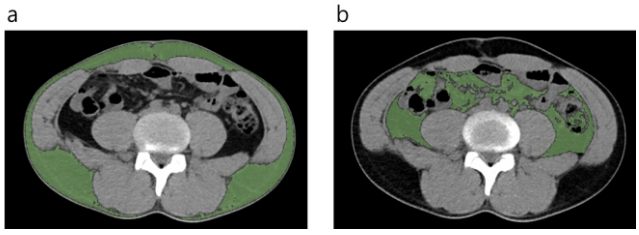

Figure 1. PET/CT image analysis of adipose tissue volume; a) subcutaneous adipose tissue (SAT) and b) visceral adipose tissue (VAT). Adipose tissue volume was measured on three consecutive slices at the level of L4/L5 intervertebral space. The areas with Hounsfield unit from -190 to -30 on CT images were automatically computed as adipose tissue in cm^3.

Results

A total of 208 subjects were enrolled in this study. Of these, 90 subjects were MHO (BMI≥25kg/m^2), and other 118 subjects were MHL (BMI<25kg/m^2) [19]. Characteristics of enrolled subjects are summarized in Table 1. Among the enrolled subjects, 94 percent are men.

In comparison of characteristics between MHO and MHL subjects, significant differences were revealed in sex, body weight, HbA1c, AST, ALT, glucose, CRP, insulin, HDL cholesterol, TG, and SUL of liver, blood pool, and muscle (P<0.05).

Table 1. *Characteristics of enrolled healthy subjects*

	Total (N=208)	MHL/subjects (N=118)	MHO/subjects (N=90)	P
Age (years)	43.08±4.01	42.89±4.07	43.32±3.93	0.442
Sex (male/female)	196/12	106/12	90/0	0.005
Height (cm)	171.51±6.98	171.46±7.58	171.59±6.14	0.890
Body weight (kg)	72.75±10.72	66.58±7.67	80.83±8.57	<0.001
HbA1c (%)	5.51±0.40	5.42±0.23	5.64±0.53	<0.001
AST (IU/l)	25.22±14.23	21.72±7.31	29.80±19.05	<0.001
ALT (IU/l)	32.13±23.80	24.08±13.68	42.70±29.55	<0.001
γ-GT (IU/l)	47.83±74.65	44.7±95.3	51.9±31.4	0.444
Glucose (mg/dL)	93.11±11.92	90.64±7.70	96.34±15.29	0.002
CRP (mg/l)	1.10±1.52	0.85±0.99	1.44±1.96	0.010
Insulin (μIU/mL)	5.85±3.58	4.46±2.44	7.68±4.00	<0.001
Total/cholesterol (mg/dL)	195.20±33.80	191.59±32.01	199.93±35.63	0.078
HDL/cholesterol (mg/dL)	53.31±14.37	57.43±15.24	47.90±11.07	<0.001
LDL/cholesterol (mg/dL)	128.68±31.04	124.11±30.19	134.68±31.28	0.015
TG (mg/dL)	135.71±83.24	113.09±63.92	165.37±95.80	<0.001
SUL of liver	2.24±0.43	2.00±0.30	2.55±0.37	<0.001
SUL of blood pool	1.61±0.36	1.42±0.23	1.86±0.34	<0.001
SUL of muscle	0.51±0.14	0.46±0.09	0.58±0.17	<0.001
Adipose/tissue volume	127.84±50.98	99.02±33.81	165.63±44.69	<0.001

MHL:metabolically healthy lean; MHL: metabolically healthy obese; WBC: white blood cell; Hb: hemoglobin; HbA1c: glycated hemoglobin; PLT: platelet; AST: aspartate aminotransferase; ALT: alanine transferase; γ-GT: gamma-glutamyl transferase; CRP: C-reactive protein; SBP: systolic blood pressure; DBP: diastolic blood pressure; HDL: high-density lipoprotein; LDL: low-density lipoprotein; TG: triglyceride; SUL: standardized uptake value normalized by lean body mass.

Metabolically healthy obese subjects had significantly more adipose tissue volume than did MHL (165.63±44.69 vs. 99.02 ±33.81, P<0.001). Furthermore, MHO subjects had significantly higher values of mean SUL of liver, blood pool, and muscle than did healthy subjects (liver, 2.55±0.37 vs. 2.00± 0.30, P<0.001; blood pool, 1.86±0.34 vs. 1.42±0.23, P<0.001; muscle, 0.58±0.17 vs. 0.46±0.09, P<0.001).

Association between SUL, clinical findings, and adipose tissue volume

Because MHO subjects had significantly higher values of mean SUL of reference organ, we conducted correlation analyses to determine if SUL of reference organs are associated with metabolic factors of the subjects.

In principle, SUL of liver, blood pool, muscle were commonly correlated with age, AST, ALT, HbA1c, insulin, CRP, and adipose tissue volume (P<0.05; Table 2). Mean SUL of li-ver was positively correlated with age, AST, ALT, HbA1c, insulin, CRP, total cholesterol, LDL cholesterol, TG, adipose tissue volume, and negatively correlated with HDL. Among those factors, adipose tissue volume revealed strongest correlation with SUL of the liver (r=0.754, P<0.001; Figure 3a). Mean SUL of blood pool was positively correlated with age, AST, ALT, HbA1c, insulin, CRP, TG, adipose tissue volume, and negatively correlated with HDL. Adipose tissue volume also revealed strongest correlation with SUL of blood pool (r=0.756)

Table 2. *Correlation analyses of SUL of liver, blood pool, and muscle with various clinical and metabolic factors.*

	SUL of liver		SUL of blood pool		SUL of muscle	
	Correlation coefficient	P	Correlation coefficient	P	Correlation coefficient	P
Age	0.161	0.020	0.182	0.008	0.174	0.012
AST	0.283	<0.001	0.324	<0.001	0.209	0.002
ALT	0.316	<0.001	0.384	<0.001	0.23	0.001
HbA1C	0.254	<0.001	0.298	<0.001	0.205	0.003
Insulin	0.539	<0.001	0.592	<0.001	0.462	<0.001
CRP	0.193	0.005	0.291	<0.001	0.289	<0.001
Total cholesterol	0.158	0.022	0.076	0.273	0.018	0.796
HDL cholesterol	-0.21	0.002	-0.226	0.001	-0.131	0.060
LDL cholesterol	0.19	0.006	0.124	0.075	0.024	0.730
TG	0.296	<0.001	0.241	<0.001	0.129	0.063
Adipose tissue volume	0.754	<0.001	0.756	<0.001	0.635	<0.001

SUL: standardized uptake value normalized by lean body mass; AST: aspartate aminotransferase; ALT: alanine transferase; HbA1c: glycated hemoglobin; CRP: C-reactive protein; HDL: high-density lipoprotein; LDL: low-density lipoprotein; TG: triglyceride.

P<0.001; Figure 3b). Mean SUL of muscle was positively correlated with age, AST, ALT, HbA1c, insulin, CRP, and adipose tissue volume. Similar to the SUL of liver and blood pool, adipose tissue volume again revealed strongest correlation with SUL of muscle (r=0.635, P<0.001; Figure 3c).

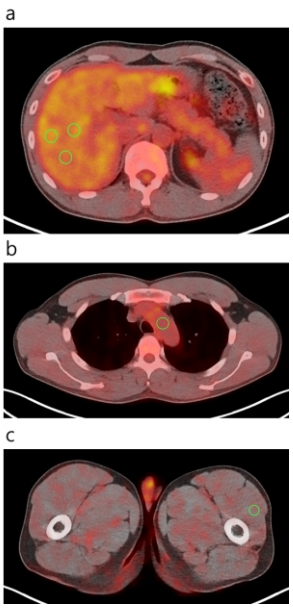

Figure 2. PET/CT image analysis of standardized uptake value of reference organ; a) liver (average value of three regions of interest (ROI) drawn in right hepatic lobe), b) blood pool (ROI in the aortic arch), and c) muscle (ROI in the vastus lateralis muscle).

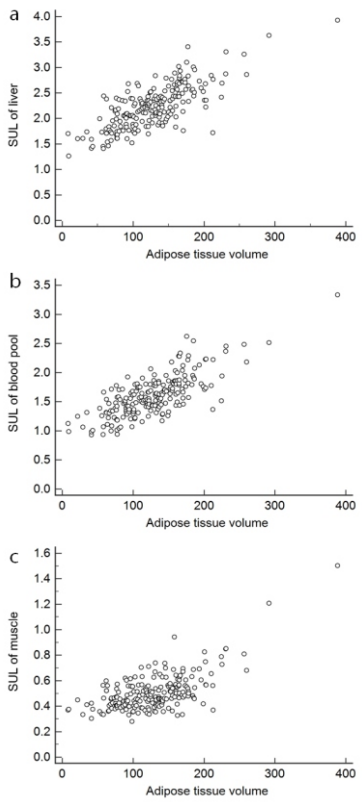

Figure 3. a) Correlation between SUL of liver and adipose tissue volume, b) Correlation between SUL of blood pool and adipose tissue volume, c) Correlation between SUL of muscle and adipose tissue volume.

Because SUL of liver, blood pool, and muscle revealed significant correlation with multiple metabolic factors, especially adipose tissue volume, we conducted multiple regression analyses to find independent predictive factors for ^{18}F-FDG uptake of reference organs (Table 3). For SUL of the liver, age, AST, ALT, HbA1c, insulin, CRP, total cholesterol, HDL cholesterol, LDL cholesterol, TG and adipose tissue volume were used as covariate; for SUL of blood pool, age, AST, ALT, HbA1c, insulin, CRP, HDL cholesterol, TG and adipose tissue volume; for SUL of muscle, age, AST, ALT, HbA1c, insulin, CRP and adipose tissue volume. Among those factors, adipose tissue volume (P<0.001) and CRP (P=0.040) were independent factors for SUL of liver. For SUL of blood pool, adipose tissue volume (P<0.001), age (P=0.045) and insulin (P<0.001) were independent factors. Only adipose tissue volume (P< 0.001) was an independent factor for SUL of muscle.

Table 3. *Multiple regression analyses for predicting SUL of liver, blood pool, and muscle*

	SUL of liver (P)	SUL of blood pool (P)	SUL of muscle (P)
Age	0.084	0.045	0.087
AST	0.229	0.083	0.844
ALT	0.954	0.573	0.360
HbA1C	0.253	0.410	0.700
Insulin	0.054	<0.001	0.117
CRP	0.040	0.974	0.298
Total cholesterol	0.916	-	-
HDL cholesterol	0.495	0.215	-
LDL cholesterol	0.977	-	-
TG	0.183	0.434	-
Adipose tissue volume	<0.001	<0.001	<0.001

SUL: standardized uptake value normalized by lean body mass; AST: aspartate aminotransferase; ALT: alanine transferase; HbA1c: glycated hemoglobin; CRP: C-reactive protein; HDL: high-density lipoprotein; LDL: low-density lipoprotein; TG: triglyceride.

Discussion

In this study, we investigated SUV of reference organ change according to clinical and metabolic factors including adipose tissue volume in healthy subjects without diabetes or dyslipidemia. Results of our study validated that SUL of liver, muscle, and blood pool in MHO subjects were significantly higher than those in MHL subjects. Besides, adipose tissue volume revealed the strongest correlation with SUL of reference organs among the metabolic factors and was an independent predictive factor for SUL of reference organs in multiple regression analysis.

Glucose metabolism of ^{18}F-FDG PET/CT can be affected by serum glucose level or body habitus [20]. Serum glucose and ^{18}F-FDG are competitively absorbed by cells; therefore, SUV can be changed by serum glucose level. In a previous study regarding correlation between patient glucose level and ^{18}F-FDG uptake, hyperglycemia can lead to decreased ^{18}F-FDG uptake of tumor [21]. To correct the influence of serum glucose for ^{18}F-FDG uptake, SUV normalized by glucose level has been suggested [22-24]. Adipose tissue reveals lower ^{18}F-FDG uptake than other organs or tissues, and for this reason, uptake of organs or tissues except adipose tissue can be overestimated in larger patients that have a higher fraction of adipose tissue [17]. A previous study reported that normalized by lean body mass or body surface area eliminates the dependence for body weight [25]. However, in this study, we found that SUV normalized by lean body mass is still affected by adipose tissue volume.

A previous study by Paquet et al. (2004) [5] demonstrated that normalized SUV by liver and blood pool are stable through sequential two PET/CT scans. They also documented that liver and blood pool are susceptible for reference organs in assessment of tumor to background ratio. Previous studies with assessing prognostic value of ^{18}F-FDG PET/CT in cancer patients revealed that tumor to liver ratios were significantly associated with clinical outcomes [9, 10]. In contrast, other previous studies revealed that weight, hepatic steatosis, CRP, and blood glucose level can affect mean SUV of liver [14, 26, 27]. Hofheinz et al. (2016) pointed out that suitability of liver as a reference organ for tumor to background ratio is limited. In their report, liver to blood ratio had fluctuation that can lead to erroneous interpretation of tumor to liver ratio value [13]. In our study, we also found that various factors including adipose tissue volume have a significant effect on SUL of the liver tissue.

Vascular ^{18}F-FDG uptake had revealed to have significant correlation with vessel wall disorder and metabolic factors. In a previous study, vascular ^{18}F-FDG uptake revealed significant correlation with the risk of atherosclerosis [15]. Another study reported that Type 2 diabetes correlates with ^{18}F-FDG uptake of carotid wall and arterial SUV is significantly higher in the diabetic group compared with the non-diabetic group [28]. Because Type 2 diabetes patients have insulin resistance, they could show normal or increased serum insulin level. Although we excluded patients with diabetes, serum insulin level still revealed significant correlation with SUL of blood pool, which corresponds to results of the previous study [28]. Still, in addition to factors associated with atherosclerosis and diabetes, adipose tissue volume revealed the strongest correlation with SUL of blood pool in the study.

According to this study, of liver, blood pool, and muscle may

be affected by adipose tissue volume, even though is normalized by lean body mass. It suggests that adipose tissue volume can influence metabolism of liver and blood pool that are often used as reference organs for normalization of ^{18}F-FDG uptake of tumor lesions. According to results of our study, metabolic activity of liver and blood pool may have limited roles due to the dependence on CRP, age and insulin, moreover, adipose tissue volume. We may need to be cautious about using tumor-to-reference organs uptake ratios in PET/CT, as those ratios can be affected by factors that are irrelevant with tumor characteristics.

Our study has several limitations. First, because of the retrospective nature of the study, we cannot evaluate intra-individual changes of SUL according to changes of body weight or adipose tissue volume. Second, most of the enrolled subjects are men, which may skew results of this study. Last, because we only enrolled healthy subjects, results of our study should be validated in further studies on patients with various diseases, especially malignant diseases.

In conclusion, adipose tissue volume can affect glucose metabolism of other organs or tissues such as liver, blood pool, and muscle in a healthy population without diabetes or dyslipidemia. Therefore, liver and blood pool may have limited roles in using as reference organs for normalization of ^{18}F-FDG uptake of the lesion.

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The authors of this study declare no conflicts of interest

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