

Original Article

Comparison of FDG-PET/CT images between chronic renal failure patients on hemodialysis and controls

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Abstract: The whole-body 2-deoxy-2-[¹⁸F]fluoro-D-glucose (FDG) distribution in chronic renal failure (CRF) patients on hemodialysis would be different from that in subjects with normal renal function, because they lack urinary FDG excretion and remain in a constant volume overload. We evaluated the difference in the physiological uptake pattern of FDG between chronic renal failure patients on hemodialysis and control subjects. The subjects for this retrospective study consisted of 24 chronic renal failure patients on hemodialysis (HD group) and 24 age- and sex-matched control subjects (NC group). Standardized uptake values normalized by the body weight (SUV_{bw}), ideal body weight (SUV_{lbw}), lean body mass (SUV_{lbm}), and body surface area (SUV_{bsa}) in the cerebellum, lungs, liver, gluteal muscles and subcutaneous fat, spleen, thoracolumbar spine, thoracic and abdominal aorta, and right atrium were calculated in positron emission tomography/computed tomography (PET/CT) images. SUV_{bw} in the gluteal muscles, subcutaneous fat, spleen and right atrium was significantly higher in the HD group as compared to that in the NC group ($p < 0.05$; unpaired t test). In addition, SUV_{lbm}, SUV_{lbw}, as well as SUV_{bsa} in the abdominal aorta were significantly higher in the HD group as compared to those in the NC group ($p < 0.05$; unpaired t test). In conclusion, as compared to normal subjects, chronic renal failure patients on hemodialysis show significantly higher physiological FDG uptake in the soft tissues, spleen and blood pool.

Keywords: Chronic renal failure, hemodialysis, FDG-PET/CT, physiological uptake

Introduction

The number of chronic renal failure (CRF) patients on hemodialysis has been increasing yearly around the world [1]. These patients have a higher overall risk of developing cancer as compared to the general populations [2].

Positron emission tomography/computed tomography (PET/CT) with 2-deoxy-2-[¹⁸F]fluoro-D-glucose (FDG) is often used for the assessment of malignant tumors. Although about 10% of the injected FDG is excreted in the urine by 70 min post injection in patients with normal kidney function [3], CRF patients on hemodialysis lack urinary FDG excretion and remain in a constant volume overload. Therefore, the whole-body FDG distribution in CRF patients on hemodialysis would be different from that in subjects with normal renal function.

Although one previous study reported establishment of a model to estimate the tissue FDG uptake in patients with renal failure, the estimation was based on theoretical assessment and not in actual patients [4]. In some previous studies, whole-body FDG distribution [5], myocardial metabolism [6], and FDG uptake in atherosclerotic plaques [7] have been evaluated in renal failure patients. However, the subjects of these studies were not on maintenance hemodialysis and had relatively mild renal failure. To the best of our knowledge, there have been no reports of evaluation of the whole-body physiological FDG uptake pattern in CRF patients on hemodialysis. To understand whole-body FDG distribution in this patient is important for appropriate evaluation of FDG-PET/CT images in these patients.

Standardized uptake value (SUV) is a semi-quantitative index of FDG uptake that is gener-

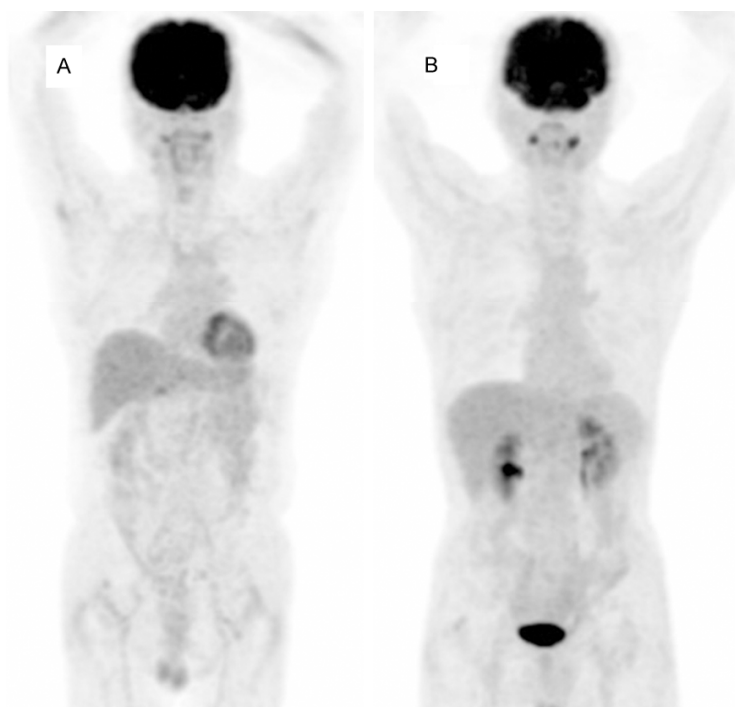


Figure 1. Representative maximum intensity projection images of FDG-PET/CT of two subjects. Both cases are 67-year-old men. Chronic renal failure patients on hemodialysis (A) lack FDG uptake in the urinary tract (kidneys, ureters, and the bladder) compared to control subjects (B).

ally used for routine clinical studies. Most commonly, SUV is normalized by the patient's body weight, using the following equation: $SUV = \text{measured activity concentration [MBq/ml]} / (\text{injected activity [MBq]} / \text{body weight [g]})$. However, this simple normalization by the body weight may not be appropriate in pediatric patients [8] or large patients who have relatively more fat in their bodies [9]. To obtain SUVs that are less dependent on the body size parameters, a few normalizing methods have been introduced [8-10]. However, it is unknown whether these methods can be used for CRF patients on hemodialysis who show different nutritional and metabolic states from patients with normal renal function.

The purpose of this study was to determine the differences in the whole-body FDG distribution between CRF patients on hemodialysis (HD group) and control subjects (NC group) in terms of the SUV normalized by the body weight, ideal body weight, lean body mass, and body surface area.

Material and methods

Our institutional review board has approved this retrospective study and the need for writ-

ten informed consent was waived (approval number: 1513).

Subjects

We initially registered 37 CRF patients on hemodialysis who underwent whole-body FDG-PET/CT at our hospital between January 2006 and March 2013. Of these, 5 patients on peritoneal dialysis and 7 patients with hyperglycemia (> 120 mg/dl) were excluded from this study. We also excluded 1 patient with sepsis who showed extremely elevated FDG uptake in the bone marrow. Finally, 24 CRF patients were included in this study as the HD group. The mean period of hemodialysis was 13.7 (range; 1-37) years and the underlying kidney diseases were as follows: chronic glomerulonephritis (8 cases), diabetes mellitus (5 cases),

nephrosclerosis (3 cases), membranous glomerulonephritis (1 case), diffuse mesangial proliferative glomerulonephritis (1 case), arteriopathic disease (1 case), drug-induced renal injury (1 case), and cause uncertain or missing (4 cases).

A total of 24 age- and sex-matched subjects who underwent FDG-PET/CT during the same period were included as the NC group. The inclusion criteria were as follows: (1) no previous history of malignancies, (2) no previous history of renal dysfunction and retained ability to evacuate the bladder before the PET/CT imaging, (3) normal blood sugar level (< 120 mg/dl), and (4) no symptoms suggestive of any inflammatory disorder at the time of the PET/CT imaging.

FDG-PET/CT protocol

After fasting for at least 4 h, the patients received an intravenous injection of ^{18}F -FDG (3.7 MBq/kg). Then, 60 min after the FDG injection, whole-body PET/CT images were obtained using a PET/CT system (Aquiduo, Toshiba Medical Systems, Tokyo, Japan) consisting of a combination of a full-ring PET scanner with lute-

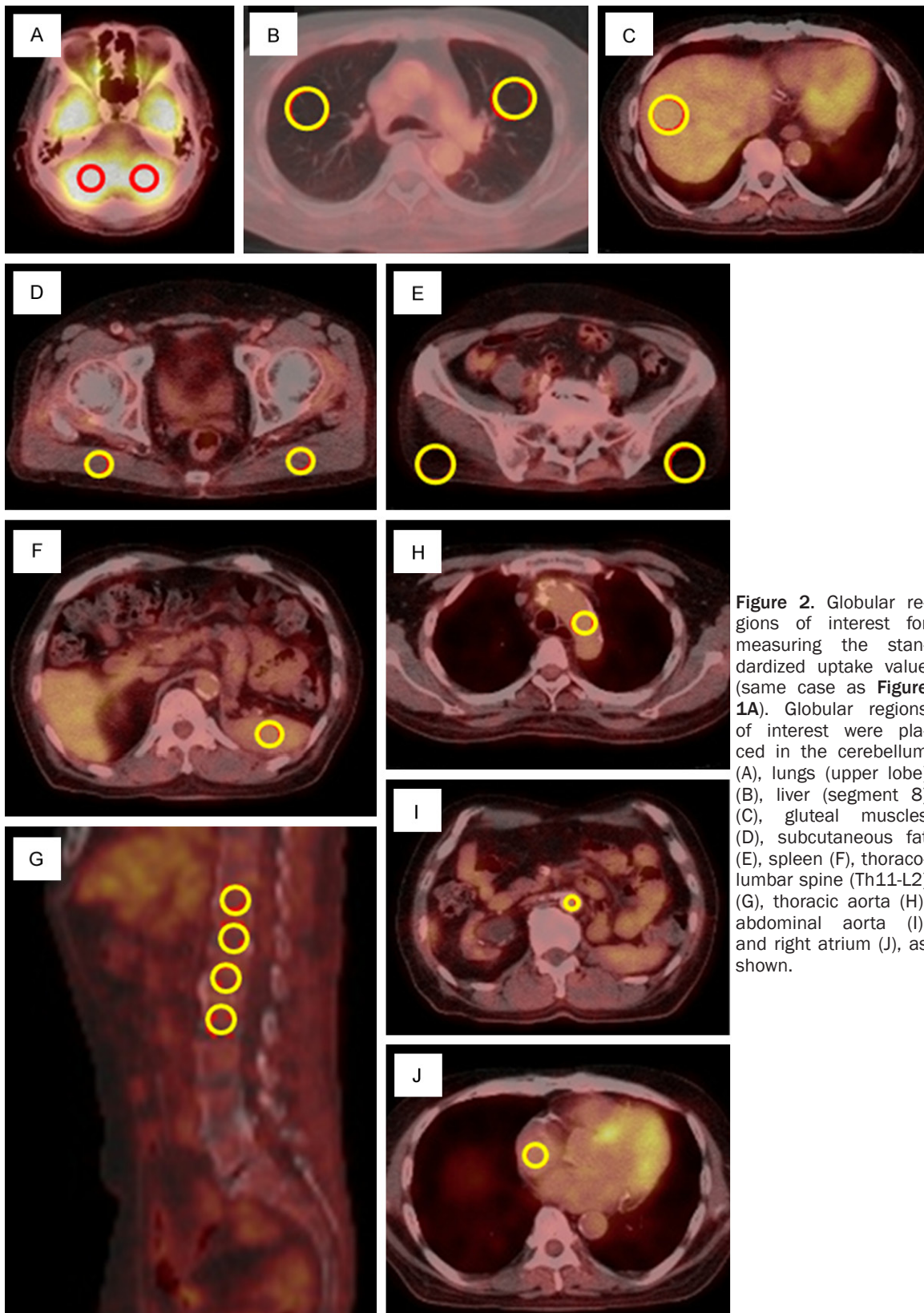


Figure 2. Globular regions of interest for measuring the standardized uptake value (same case as **Figure 1A**). Globular regions of interest were placed in the cerebellum (A), lungs (upper lobe) (B), liver (segment 8) (C), gluteal muscles (D), subcutaneous fat (E), spleen (F), thoracolumbar spine (Th11-L2) (G), thoracic aorta (H), abdominal aorta (I), and right atrium (J), as shown.

tium oxyorthosilicate crystals and a 16-row helical CT scanner. CT studies for attenuation

correction were performed under expiratory breath-holding using the following parameters:

120 kV, 50-200 mAs, field of view 500 mm, pitch 15.0, and slice thickness 2.0 mm. PET emission data were obtained under free-breathing using the following parameters: 3D mode, 2 min per bed position (for 6-8 bed positions), matrix size 128 × 128, and Gaussian filter size 5 mm. All patients drank approximately 300 ml of water after the FDG injection for oral hydration and gastric dilatation. The subjects were instructed to evacuate their bladder just before the PET/CT imaging. No contrast media were used.

Figure 1 shows maximum intensity projection images of representative cases from the HD and NC groups.

Regions of interest for SUV measurements

On the fused PET/CT images, one nuclear medicine physician and one radiologist placed, by consensus, globular regions of interest (ROI) in the cerebellum, lungs (upper lobe), liver (segment 8), gluteal muscles and subcutaneous fat, spleen, thoracolumbar spine (Th11-L2), thoracic and abdominal aorta, and right atrium. The diameters of the ROIs were 3 cm in both lungs, liver, and bilateral gluteal subcutaneous fat; 2 cm in bilateral cerebellar hemispheres, bilateral gluteus maximus muscles, spleen, Th11-L2 vertebral bodies, thoracic aorta (distal arch), and right atrium; 1 cm in the abdominal aorta (at the level of the renal arteries). If placing of ROI on the gluteal maximus muscles and subcutaneous fat was difficult because of muscular atrophy or a thin body, the diameter of the ROI was reduced to a minimum of 1 cm. **Figure 2** shows a representative illustrating the ROIs.

Although each ROI was carefully placed so as not to include any diseases or adjacent organs, placing of the ROI proved difficult in some organs in the HD group. Therefore, one right cerebellar hemisphere (old infarction), one right lung (pneumothorax), gluteal subcutaneous fat of either side in one patient (thin body), one spleen (previous splenectomy), one thoracolumbar spine (previous vertebroplasty), one thoracic aorta (aneurysm), two abdominal aortas (aneurysm and previous endovascular aneurysm repair), and two right atria (cardiac pacemaker insertion) were excluded from the analysis in the HD group. In the NC group, we were able to place the ROIs appropriately in all organs in all subjects.

In addition, we calculated the maximum SUV in the bladder urine, normalized by the body weight (SUV_{bw}). However, 5 patients of the HD group in whom FDG uptake in the bladder could not be detected by visual interpretation were excluded.

SUV measurements and normalization

The mean SUV_{bw} for each of the ROIs was calculated for all subjects. For the case of the thoracolumbar spine, the highest SUV_{bw} among the Th11-L2 vertebral bodies was selected for the following evaluations. The obtained SUV_{bw} was converted to SUVs normalized by the ideal body weight (SUV_{ibw}), lean body mass (SUV_{lbm}), and body surface area (SUV_{bsa}) using the following equations [9-11]:

Ideal body weight [kg] for men = $48.0 + 1.06 \times (\text{height [cm]} - 152.0)$

Ideal body weight [kg] for women = $45.5 + 0.91 \times (\text{height [cm]} - 152.0)$ (If the ideal body weight was greater than the weight, the ideal body weight was equal to the weight.)

Lean body mass [kg] for men = $1.10 \times \text{weight [kg]} - 120 \times (\text{weight [kg]} / \text{height [cm]})^2$

Lean body mass [kg] for women = $1.07 \times \text{weight [kg]} - 148 \times (\text{weight [kg]} / \text{height [cm]})^2$

Body surface area [m^2] = $(\text{weight [kg]})^{0.425} \times (\text{height [cm]})^{0.725} \times 0.007184$

$SUV_{ibw} = SUV_{bw} \times (\text{ideal body weight [kg]} / (\text{body weight [kg]}))$

$SUV_{lbm} = SUV_{bw} \times (\text{lean body mass [kg]} / (\text{body weight [kg]}))$

$SUV_{bsa} = SUV_{bw} \times (\text{body surface area [m}^2\text{]} / (\text{body weight [kg]}))$

Statistical analysis

All numerical values are expressed as mean \pm standard deviation. The differences in the clinical characteristics between the HD and NC groups were analyzed by student's *t* test. The mean SUV_{bw} , SUV_{ibw} , SUV_{lbm} , and SUV_{bsa} of each organs were compared between the HD and NC groups by an unpaired *t*-test. Differences with $p < 0.05$ were considered to be significant.

Table 1. Clinical characteristics of subjects

Group	HD	NC	p
Number	24	24	-
Male : Female	15:9	15:9	-
Age (y)	62.5 ± 10.8	62.5 ± 11.8	0.824
Height (cm)	161.1 ± 9.5	163.4 ± 9.5	0.408
Body weight (kg)	51.8 ± 12.1	62.5 ± 11.8	0.003*
Injection-scan time (min)	68.1 ± 7.9	66.1 ± 7.3	0.377
Blood sugar level (mg/dl)	94.3 ± 14.6	96.5 ± 10.0	0.552

* $p < 0.05$ (student's t test). Notes: HD = chronic renal failure patients on hemodialysis; NC = control subjects.

Results

The clinical characteristics of the HD and NC groups are shown in **Table 1**. The body weight in the HD group was significantly lower than that in the NC group ($p = 0.003$). The height, injection-scan time, and blood sugar level were not significantly different between the two groups.

Table 2 shows mean SUV_{bw} , SUV_{ibw} , SUV_{ibm} , and SUV_{bsa} in each of the organs in the HD and NC groups. The SUV_{bw} in the gluteus maximus muscle of both sides, gluteal subcutaneous fat of both sides, spleen, and right atrium was significantly higher in the HD group than those in the NC group. In addition, the SUV_{ibm} , SUV_{ibw} , and SUV_{bsa} in the abdominal aorta were also higher in the HD group as compared to the NC group. For the case of the thoracic aorta, only the SUV_{bsa} showed significant difference between the HD and NC groups. No significant differences in the values between the two groups were observed in the cerebellar hemisphere, lungs, liver and thoracolumbar spine.

The maximum SUV_{bw} in the bladder urine was 2.69 ± 1.68 in the HD group and 25.3 ± 18.7 in the NC group. There was significant difference between the two groups ($p < 0.001$).

Discussion

This was the first study conducted to evaluate the physiological FDG uptake pattern in CRF patients on hemodialysis. In these patients, the SUV_{bw} in the gluteus maximus muscle, gluteal subcutaneous fat, and the right atrium were significantly higher as compared to the values in the control subjects. Given the insulin resistance in patients with kidney disease [12], the higher FDG uptake in the soft tissues may be

an unexpected result. Although we cannot explain the mechanism from this study, these results indicate that the injected FDG, which should be excreted in the urine, accumulates in the soft tissues in CRF patients on hemodialysis. On the other hand, our finding of a higher SUV_{bw} in the right atrium in the HD group as compared to that in the NC group was concordant with the previously published result by Derlin et al, who measured the SUV_{bw} in the mid lumen of the upper and lower vena cava [7]. These findings suggest that the FDG accumulation in the central venous system may reliably reflect the degree of volume overload in CRF patients.

In our study, the splenic SUV_{bw} also differed significantly between the HD and NC groups. In the HD group, two subjects had chronic hepatitis C and one was a silent hepatitis B carrier. However, we believe that hepatitis virus alone cannot explain our result, because of the small number of subjects with the virus. Patients on hemodialysis are known to have a high incidence of bacterial infections [13]. In these patients, the immune functions of the spleen may be activated by frequent exposure to potential infectious risk factors, such as repeated disruption of the skin barrier.

Because the reduced protein and energy intakes in CRF patients contribute to the decline in many of the nutritional measures [14], the body weight in the HD group was significantly lower than that in the NC group, as shown in **Table 1**. We expected that SUV normalization by the body size parameters had somewhat of an impact on the whole-body FDG uptake in the HD group. Consequently, the SUV_{ibw} , SUV_{ibm} , and SUV_{bsa} in the abdominal aorta differed significantly between the HD and NC groups. Furthermore, SUV_{bsa} of the thoracic aorta in the HD group was significantly higher than that in the NC group. Although our findings of the absence of any significant difference in the SUV_{bw} in the arterial blood pool (thoracic and abdominal aorta) between the HD and NC groups was discordant with the previous report by Minamimoto et al [5], FDG accumulation in the arterial blood pool should be elevated in CRF patients, based on our results of the analyses using the body size parameters.

Table 2. Standardized uptake values of each organs

Group	HD	NC	p
Right cerebellar hemisphere	(n = 23)	(n = 24)	
SUV _{bw}	6.65 ± 1.94	7.27 ± 1.14	0.194
SUV _{ibw}	6.43 ± 1.97	6.70 ± 1.12	0.574
SUV _{lbm}	5.48 ± 1.52	5.72 ± 0.95	0.531
SUV _{bsa}	0.198 ± 0.053	0.196 ± 0.028	0.887
Left cerebellar hemisphere	(n = 24)	(n = 24)	
SUV _{bw}	6.68 ± 1.93	7.41 ± 1.23	0.123
SUV _{ibw}	6.46 ± 1.95	6.82 ± 1.16	0.444
SUV _{lbm}	5.51 ± 1.52	5.82 ± 1.00	0.396
SUV _{bsa}	0.198 ± 0.053	0.200 ± 0.030	0.890
Right lung	(n = 23)	(n = 24)	
SUV _{bw}	0.31 ± 0.10	0.35 ± 0.07	0.156
SUV _{ibw}	0.30 ± 0.09	0.32 ± 0.06	0.413
SUV _{lbm}	0.26 ± 0.08	0.27 ± 0.05	0.421
SUV _{bsa}	0.009 ± 0.002	0.009 ± 0.002	0.852
Left lung	(n = 24)	(n = 24)	
SUV _{bw}	0.35 ± 0.11	0.38 ± 0.10	0.292
SUV _{ibw}	0.34 ± 0.10	0.35 ± 0.08	0.665
SUV _{lbm}	0.29 ± 0.09	0.30 ± 0.07	0.695
SUV _{bsa}	0.010 ± 0.002	0.010 ± 0.002	0.935
Liver	(n = 24)	(n = 24)	
SUV _{bw}	2.23 ± 0.39	2.39 ± 0.28	0.104
SUV _{ibw}	2.15 ± 0.42	2.20 ± 0.26	0.678
SUV _{lbm}	1.85 ± 0.33	1.88 ± 0.23	0.700
SUV _{bsa}	0.066 ± 0.010	0.065 ± 0.005	0.415
Right gluteal muscle	(n = 24)	(n = 24)	
SUV _{bw}	0.67 ± 0.14	0.60 ± 0.10	0.048*
SUV _{ibw}	0.65 ± 0.14	0.55 ± 0.08	< 0.01*
SUV _{lbm}	0.56 ± 0.12	0.47 ± 0.08	< 0.01*
SUV _{bsa}	0.020 ± 0.004	0.016 ± 0.002	< 0.01*
Left gluteal muscle	(n = 24)	(n = 24)	
SUV _{bw}	0.66 ± 0.14	0.59 ± 0.08	0.036*
SUV _{ibw}	0.64 ± 0.15	0.54 ± 0.06	< 0.01*
SUV _{lbm}	0.55 ± 0.12	0.46 ± 0.06	< 0.01*
SUV _{bsa}	0.020 ± 0.003	0.016 ± 0.002	< 0.01*
Right subcutaneous fat	(n = 23)	(n = 24)	
SUV _{bw}	0.46 ± 0.25	0.29 ± 0.18	0.012*
SUV _{ibw}	0.44 ± 0.24	0.27 ± 0.19	< 0.01*
SUV _{lbm}	0.39 ± 0.22	0.23 ± 0.16	< 0.01*
SUV _{bsa}	0.014 ± 0.007	0.008 ± 0.006	< 0.01*
Left subcutaneous fat	(n = 23)	(n = 24)	
SUV _{bw}	0.45 ± 0.26	0.29 ± 0.19	0.021*
SUV _{ibw}	0.44 ± 0.25	0.28 ± 0.19	0.016*
SUV _{lbm}	0.38 ± 0.22	0.24 ± 0.17	0.016*
SUV _{bsa}	0.014 ± 0.008	0.008 ± 0.006	< 0.01*
Spleen	(n = 23)	(n = 24)	
SUV _{bw}	2.08 ± 0.38	1.88 ± 0.25	0.039*

In other organs, the SUV_{ibw}, SUV_{lbm}, and SUV_{bsa} showed similar trends to those of the SUV_{bw}. The body weight was equal to the ideal body weight in 18/24 patients (75.0%) of the HD group, but in only 6/24 subjects (25.0%) of the NC group. Therefore, the SUV_{ibw} may be meaningless, particularly in CRF patients on hemodialysis. Recently, use of SUV_{lbm} has been spreading for monitoring of the responses to anticancer therapy (PERCIST) [15]. The hepatic SUV_{lbm}, which is the reference organ in PERCIST, did not differ significantly between the HD and NC groups. However, the effects of elevated FDG uptake in the background organs or blood pool may influence the judge of the therapeutic effect. Further studies will be needed to confirm the applicability of PERCIST in CRF patients on hemodialysis.

Our study has some limitations. First, because not all subjects in the NC group gave blood samples, there remains the possibility of inclusion of some patients with mild renal failure in the NC group as well. However, all the subjects in the NC group could evacuate their bladder prior to the PET/CT imaging and showed significantly higher FDG uptake in their bladder urine (maximum SUV_{bw} was 25.3 ± 18.7). Therefore, we believe that these subjects were applicable for comparison with CRF patients on hemodialysis. Second, because most patients in the HD group had been undergoing hemodialysis at another hospital, the interval between the FDG-PET/CT and the last hemodialysis was not uniform, and information about the protocol of hemodialysis

SUV _{ibw}	2.01 ± 0.36	1.73 ± 0.24	< 0.01*
SUV _{lbm}	1.73 ± 0.29	1.48 ± 0.21	< 0.01*
SUV _{bsa}	0.062 ± 0.009	0.051 ± 0.004	< 0.01*
Thoracolumbar spine	(n = 23)	(n = 24)	
SUV _{bw}	1.85 ± 0.54	1.80 ± 0.32	0.693
SUV _{ibw}	1.78 ± 0.50	1.66 ± 0.33	0.350
SUV _{lbm}	1.52 ± 0.41	1.42 ± 0.28	0.304
SUV _{bsa}	0.055 ± 0.013	0.049 ± 0.008	0.054
Thoracic aorta	(n = 23)	(n = 24)	
SUV _{bw}	1.73 ± 0.36	1.67 ± 0.21	0.488
SUV _{ibw}	1.67 ± 0.34	1.54 ± 0.21	0.102
SUV _{lbm}	1.43 ± 0.28	1.31 ± 0.18	0.084
SUV _{bsa}	0.052 ± 0.010	0.045 ± 0.005	< 0.01*
Abdominal aorta	(n = 22)	(n = 24)	
SUV _{bw}	1.80 ± 0.35	1.70 ± 0.20	0.265
SUV _{ibw}	1.74 ± 0.34	1.56 ± 0.19	0.041*
SUV _{lbm}	1.48 ± 0.27	1.33 ± 0.16	0.032*
SUV _{bsa}	0.053 ± 0.009	0.046 ± 0.004	< 0.01*
Right atrium	(n = 22)	(n = 24)	
SUV _{bw}	1.82 ± 0.32	1.59 ± 0.21	< 0.01*
SUV _{ibw}	1.75 ± 0.32	1.42 ± 0.22	< 0.01*
SUV _{lbm}	1.50 ± 0.26	1.21 ± 0.17	< 0.01*
SUV _{bsa}	0.054 ± 0.008	0.043 ± 0.005	< 0.01*

*p < 0.05 (unpaired t test). Notes: HD = chronic renal failure patients on hemodialysis; NC = control subjects; SUV = standardized uptake value normalized by the body weight (SUV_{bw}), the ideal body weight (SUV_{ibw}), lean body mass (SUV_{lbm}), and body surface area (SUV_{bsa}). All SUVs are mentioned as mean ± standard deviation.

sis and nutritional status was insufficient. The other limitations were the small sample size and retrospective design of the study.

In conclusion, CRF patients on hemodialysis show significantly higher physiological FDG uptake in the soft tissues, spleen, and the blood pool as compared to normal subjects.

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Disclosure of conflict of interest

The authors declare that they have no conflict of interest.

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