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Original

Increased physiological [^{18}F]FDG uptake in the liver and blood pool among patients with impaired renal function

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Abstract

Background: In the daily clinical course, the liver uptake may seem to be increased in patients with renal failure. The purpose of this study was to investigate whether or not the FDG uptake of the liver, and the FDG uptake of blood pool which is generally used as a reference site as well as liver, is increased in patients with renal failure.

Material and methods: We retrospectively analyzed 233 patients who underwent FDG positron emission tomography/computed tomography (PET/CT). Renal failure is defined as an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2. We compared the FDG uptake in the liver and mediastinal blood pool of 67 patients with impaired renal function to that in 166 patients with a normal renal function (eGFR ≥ 60 mL/min/1.73 m^2). Correlations between the liver or mediastinal blood pool FDG uptake and the eGFR were also analyzed by Spearman's correlation test.

Results: Maximum and mean standardized uptake values (SUV_{max} and SUV_{mean}, respectively) of the liver and the SUV_{mean} of the mediastinal blood pool were 3.48 ± 0.57, 2.56 ± 0.37, and 1.90 ± 0.28 in the impaired renal function group, respectively, and 3.13 ± 0.45, 2.29 ± 0.33, and 1.66 ± 0.23, in the normal group, respectively. The SUV_{max} and SUV_{mean} of the liver and SUV_{mean} of the mediastinal blood pool in the impaired renal function group were significantly higher than those in the normal group ($p < 0.001$, < 0.001, and < 0.001, respectively). The SUV_{max} and SUV_{mean} of the liver and SUV_{mean} of the mediastinal blood pool of patients showed a significant negative correlation with the eGFR (Spearman's $p = -0.25$, -0.30, and -0.40, respectively, each $p < 0.001$).

Conclusions: FDG uptake in both the liver and mediastinal blood pool was higher in patients with impaired renal function.

KEY words: renal failure; eGFR; liver; mediastinal blood pool; FDG

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Introduction

[^{18}F] fluoro-2-deoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) is a hybrid imaging method clinically used as an effective, non-invasive imaging tool for assessing various neoplastic diseases [1–4]. In the clinical course, both the visual assessment of FDG uptake in the tumor and the quantitative assessment of FDG uptake in the tumor lesions are performed using the standardized uptake values (SUV) [5, 6]. During the assessment of tumor uptake in malignant lymphoma, the liver and blood pool of the mediastinum are used as reference sites [7–9]. In daily clinical use, the liver uptake appears to be increased in patients with impaired renal function. Given that the FDG uptake in the liver and mediastinal blood pool is often used as a reference region for evaluating the tumor activity, it is important to understand the influencing factors. This study aimed to clarify if the FDG uptake in the liver and mediastinal blood pool in patients with impaired renal function is increased compared to that in patients with normal renal function.

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Table 1. Clinical characteristics of the study groups

	Patients with impaired renal function (eGFR < 60 mL/min/1.73 m^2; n = 67)	Patients with normal renal function (eGFR ≥ 60 mL/min/1.73m^2; n = 166)	p-value
Age [years]	70.8 ± 10.2	66.3 ± 13.2	0.006*
Gender			0.810
Female	29	69	
Male	38	97	
Weight [kg]	58.8 ± 12.1	55.1 ± 10.7	0.021*
Blood glucose [mg/dL]	104.4 ± 13.5	103.8 ± 13.2	0.752
FDG [MBq]	182.8 ± 40.1	170.8 ± 37.8	0.033*
eGFR [mL/min/1.73 m^2]	45.3 ± 11.3	78.1 ± 13.9	< 0.001*
GOT (IU/L) [13–30]	21.8 ± 7.9	21.2 ± 6.5	0.547
GPT (IU/L) [7–23]	16.7 ± 10.8	15.8 ± 7.0	0.509
T-Bil (mg/dL) [0.4–1.5]	0.69 ± 0.27	0.66 ± 0.24	0.514
Alb (g/dL) [4.0–5.2]	3.9 ± 0.5	3.9 ± 0.5	0.967
TP (g/dL) [6.5–8.0]	6.9 ± 0.6	7.0 ± 0.5	0.113

*Data are represented as the mean ± standard deviation; A p-value < 0.05 was considered statistically significant; FDG — fluorodeoxyglucose; eGFR — estimated glomerular filtration rate; GOT — glutamic oxaloacetic transaminase; GPT — glutamic pyruvic transaminase; T-Bil — total bilirubin; Alb — albumin; TP — total protein

Material and methods

Procedures and population

This retrospective study was approved by the Ethics Committee of Tokushima University Hospital (approval number: 3210). The need for written informed patient consent was waived due to the study's retrospective design. All methods were carried out in accordance with relevant guidelines and regulations. We identified retrospectively patients who underwent FDG PET/CT from January 2018 to June 2018 and who had renal function test values measured within one month of the FDG PET/CT.

We excluded patients with a history of primary liver tumor, liver metastasis, or liver invasion; liver mass lesion detectable on PET/CT; suspected cirrhosis; fatty liver (less than 40 Hounsfield units on CT); diabetes mellitus; blood glucose level of 140 mg/dL or higher before FDG injection; and PET/CT within 3 months of chemotherapy, radiation therapy, or a surgical procedure. Finally, 233 patients (male, n = 135; female, n = 98; mean age, 67.6 years) were included in this study.

The KDIGO CKD Work Group clinical practice guidelines define chronic kidney disease as decreased kidney function shown by a glomerular filtration rate of < 60 mL/min/1.73 m^2, kidney damage markers, or both of at least three months duration, regardless of the underlying cause [10]. Based on this guideline, patients with an estimated glomerular filtration rate (eGFR) of < 60 mL/min/1.73 m^2 were suspected of having, CKD. We used that definition to identify patients with impaired renal function.

We compared the FDG uptake in the liver and mediastinal blood pool of 67 patients with impaired renal function to that in 166 patients with normal renal function (eGFR ≥ 60 mL/min/1.73 m^2). Liver function test values (glutamic oxaloacetic transaminase [GOT], glutamic pyruvic transaminase [GPT], and total bilirubin [T-Bil]), renal function test values (eGFR) and serum albumin and total protein measured within one month of the FDG PET/CT were compared between these groups. Correlations between eGFR and, individually, the liver uptake and mediastinal blood pool uptake were also calculated.

The evaluation of the FDG uptake in the liver and mediastinal blood pool of the study group

PET/CT images were retrospectively evaluated using the image viewer (AW server 2.0; GE Healthcare, Milwaukee, WI, USA) by board-certified nuclear medicine physicians. The maximum and mean standardized uptake values (SUV_{max} and SUV_{mean}) of the liver and SUV_{mean} of the mediastinal blood pool were calculated. The SUV_{max} and SUV_{mean} of the liver were calculated by automatically setting a volume of interest (VOI) in the liver of the study group using AW server 2.0 [5]. For the mediastinal blood pool SUV_{mean}, a 1-cm-diameter spherical VOI was set in the descending aorta to not overlap with the blood vessel wall [11].

Statistical analyses

Data are expressed as the mean ± standard deviation. The homogeneity of variance was assessed using Levene's test. The Kolmogorov–Smirnov test was used to determine which variables were normally distributed. For normally distributed variables, differences in the parameter variables were evaluated using Student's t-test, whereas non-normally distributed variables were evaluated using Welch's t-test. We quantified the relationship between liver and blood pool uptake and eGFR using Spearman's correlation analysis. Statistical analyses were performed using the SPSS Statistics software program (version 24; IBM, Chicago, IL, USA). A p-value of less than 0.05 was considered statistically significant.

Results

A comparison of the clinical characteristics related to PET/CT and the liver function test data, serum albumin, and total protein of the patients with impaired renal function and the data of those with normal renal function are shown in Table 1. While each group's mean serum albumin was slightly lower than the normal limit, the mean serum GOT, GPT, T-Bil, and total protein levels of each group were within the normal ranges. A comparison of the liver and mediastinal blood uptake data of the patients with impaired renal function and the data of those with normal renal function are shown in Table 2.

Table 2. Comparison of the FDG uptake in the liver and mediastinal blood between patients with impaired renal function and normal renal function levels

Parameter	Patients with impaired renal function (eGFR < 60 mL/min/1.73 m^2; n = 67)	Patients with normal renal function (eGFR ≥ 60 mL/min/1.73 m^2; n = 166)	p-value
Liver			
SUV_{max}	3.48 ± 0.57	3.13 ± 0.45	< 0.001*
SUV_{mean}	2.56 ± 0.37	2.29 ± 0.33	< 0.001*
Blood pool			
SUV_{mean}	1.90 ± 0.28	1.66 ± 0.23	< 0.001*

*Data are represented as the mean ± standard deviation; A p-value < 0.05 was considered statistically significant; eGFR — estimated glomerular filtration rate; SUV_{max} — maximum standardized uptake value; SUV_{mean} — mean standardized uptake value

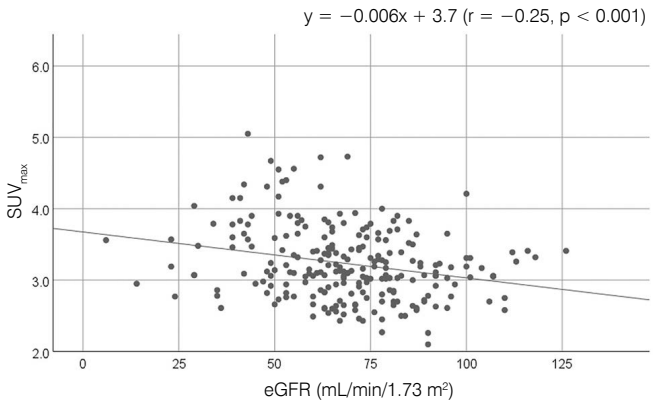

Figure 1. The correlation between eGFR and the liver SUV_{max}, eGFR demonstrated a significantly negative but weak correlation with the liver SUV_{max}, showing a regression line of y = –0.006x + 3.7 (r = –0.25, p < 0.001)

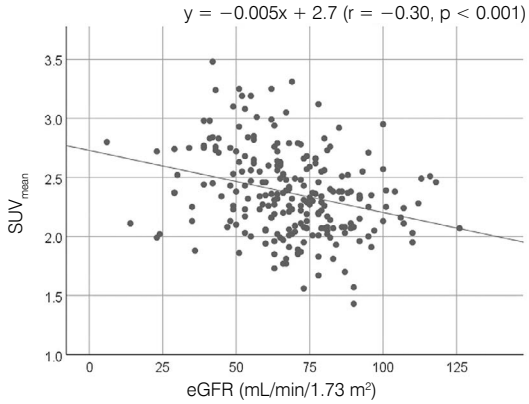

Figure 2. The correlation between eGFR and liver SUV_{mean}, eGFR demonstrated a significantly negative but weak correlation with the liver SUV_{mean}, showing a regression line of y = –0.005x + 2.7 (r = –0.30, p < 0.001)

The SUV_{max} and SUV_{mean} of the liver and the SUV_{mean} of the mediastinal blood pool in the impaired renal function group were 3.48 ± 0.57, 2.56 ± 0.37, and 1.90 ± 0.28, respectively; these values in the normal group were 3.13 ± 0.45, 2.29 ± 0.33, and 1.66 ± 0.23, respectively. The SUV_{max} and SUV_{mean} of the liver and SUV_{mean} of the mediastinal blood pool (p < 0.001, < 0.001, and < 0.001, respectively) were significantly different between the two groups. The eGFR had a negative, but weak, correlation with liver SUV_{max}, with a regression line of y = −0.006x + 3.7 (r = −0.25, p < 0.001) (Fig. 1). Furthermore, eGFR had a similar negative, but weak, correlation with the liver SUV_{mean}, with a regression line of y = −0.005x + 2.7 (r = −0.30, p < 0.001) (Fig. 2). The eGFR had a negative and moderate correlation, which was significant, with the SUV_{mean} of the mediastinal blood pool, with a regression line of y = −0.005x + 2.1 (r = −0.40, p < 0.001) (Fig. 3). Figure 4 shows the representative PET/CT images of a patient with impaired renal function, showing increased liver and mediastinal blood uptake. Figure 5 shows the representative PET/CT images of a patient with a normal renal function level.

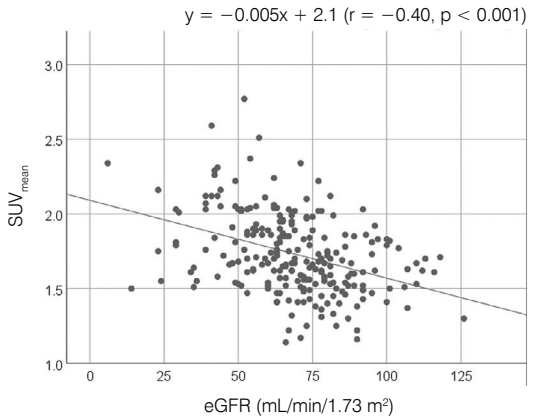

Figure 3. The correlation between eGFR and the SUV_{mean} of the mediastinal blood pool. eGFR demonstrated a significantly negative and moderate correlation with the SUV_{mean} of the mediastinal blood pool, showing a regression line of y = –0.005x + 2.1 (r = –0.40, p < 0.001)

Discussion

The SUV_{max} and SUV_{mean} of the liver and SUV_{mean} of the mediastinal blood pool in the impaired renal function group were significantly higher than those in the normal group. The eGFR showed a weak but significant negative correlation with the liver SUV_{max} and SUV_{mean}. Furthermore, eGFR was significantly negatively correlated with the SUV_{mean} of the mediastinal blood pool. There is no consensus on the FDG uptake in the liver and blood pool in patients with impaired renal function. A previous study stated that 12 patients with impaired renal function (eGFR < 60 mL/min) exhibited no significant differences in FDG uptake in the liver and

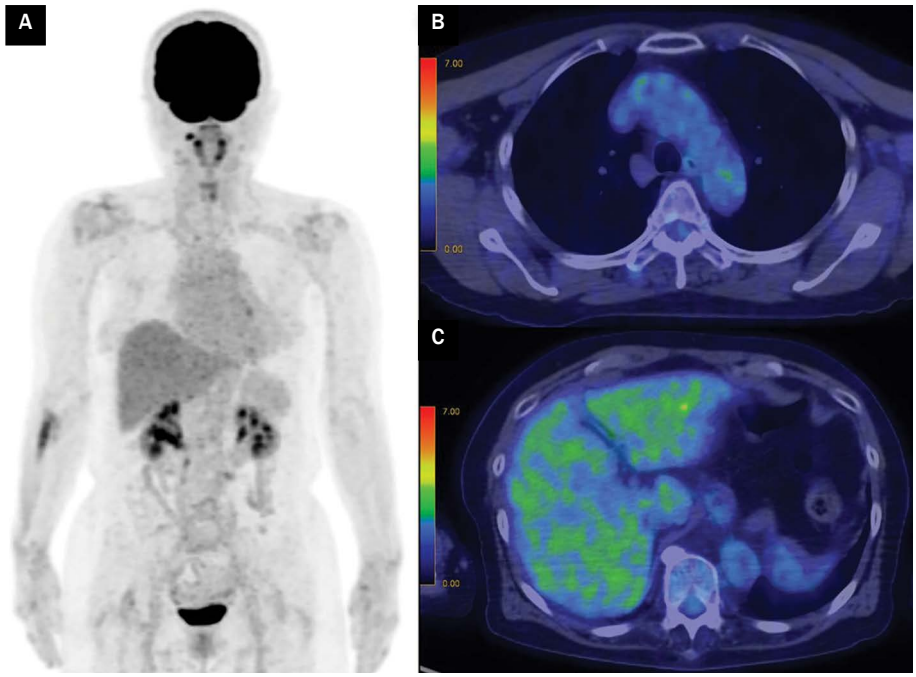

Figure 4. PET/CT image of a representative case with impaired renal function showing increased liver and mediastinal blood uptake. Maximum intensity projection of FDG PET (**A**), PET/CT fusion image of mediastinal blood pool (**B**), PET/CT fusion image of liver (**C**) of a 70-year-old female patient with impaired renal function (eGFR: 48 mL/min/1.73 m^2). Parameters of interest were as follows: SUV_{max} of 4.3, SUV_{mean} of 2.8 in liver, SUV_{mean} of 1.9 in mediastinal blood pool

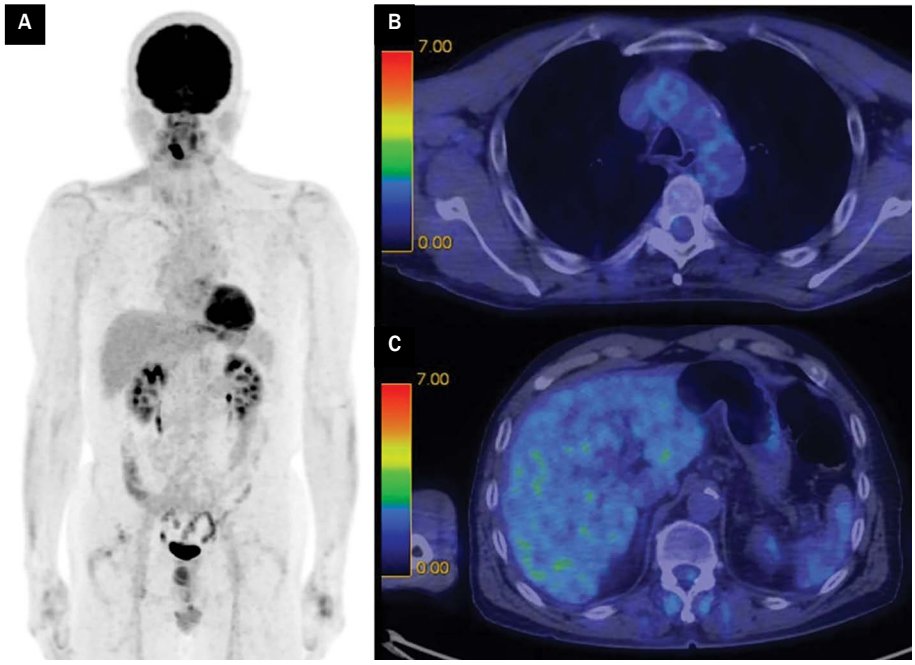

Figure 5. PET/CT image of a representative case with normal renal function. Maximum intensity projection of FDG PET (**A**), PET/CT fusion image of mediastinal blood pool (**B**), PET/CT fusion image of liver (**C**) of a 60-year-old male patient with normal renal function (eGFR: 79 mL/min/1.73 m^2). Parameters of interest were as follows: SUV_{max} of 3.0, SUV_{mean} of 2.1 in liver, SUV_{mean} of 1.6 in mediastinal blood pool

blood pool compared with patients with normal renal function [12]. Another study reported that FDG uptake in the liver in 30 patients with impaired renal function was higher than in patients with normal renal function; however, there was no significant difference (liver SUV_{max} 2.90 *vs.* 2.60, respectively. p=0.62) [13]. Lastly, a paper reported that the SUV_{mean} of the left atrium as a cardiac blood pool in 20 patients with impaired renal function and a blood serum creatinine level over 1.1 mg/dL was significantly higher than that in

20 healthy volunteers (SUV_{mean} 1.5 ± 0.2 *vs.* 1.3 ± 0.1, respectively $p < 0.05$) [14]. This same study also reported that the SUV_{mean} of the liver in patients with impaired renal function was higher than in healthy volunteers, but not significant (SUV_{mean} 1.8 ± 0.4 *vs.* 1.7 ± 0.3, respectively). The present article is the first report which showed uptakes in both the liver and the mediastinal blood pool in the impaired renal function group were significantly higher than those in the normal group. Our study included more patients than did previous studies, strengthening the level of evidence.

The potential explanation for why the uptake in the liver and mediastinal blood pool is significantly higher in patients with impaired renal function is thought to be that radiopharmaceuticals (FDG) remain in the blood because of lower renal metabolism and less urinary excretion in patients with impaired renal function. Therefore, the uptake in the blood pool becomes slightly higher. Since many blood vessels are stretched in the liver, it is considered that the uptake in the liver becomes slightly higher if there is a relatively higher concentration in the blood.

In this study, no strong effect of renal function decline on the liver uptake and blood pool uptake was observed; however, uptake in these sites in the impaired renal function group was significantly higher than in the normal group. The target tumor lesion is usually compared with the normal uptake in the surrounding background or by referencing the uptake in the mediastinal blood pool or the liver [15, 16]. It may be necessary to recognize impaired renal function as one factor which affects the liver and blood pool uptake and its use as the reference.

Some factors that can affect liver uptake in FDG PET/CT have been previously reported. Abele et al. [17] reported that on CT there was no association between liver attenuation and liver SUV_{mean}. On the other hand, Keramida et al. [18] reported increased FDG uptake into fatty liver. Liu et al. [19] reported that moderate fatty liver positively affected liver FDG uptake, while severe fatty liver negatively affected it. Patients with fatty liver were excluded from the present study. It has been reported that hypoglycemia appeared to reduce liver and blood pool activity [20]. In our study, no significant difference in blood sugar level between patients with normal renal function and impaired renal function was observed. It also has been reported that the liver SUV_{max} and SUV_{mean} of patients with hypoalbuminemia derived from malnutrition were significantly lower than those of individuals with normal serum albumin levels [21]. In this study, no significant difference in the serum albumin and total protein level between patients with impaired renal function and normal renal function was observed; hence, the effect of hypoalbuminemia on hepatic uptake seemed almost negligible.

Our study has a few limitations. First, the retrospective study design may predispose to selection bias. Second, the VOI was set when measuring liver uptake, and it is possible that the VOI might contain hidden liver lesions. Patients with detectable liver lesions were excluded from the analysis in this study. However, our study may still have included patients with small cystic lesions, liver hemangiomas, vascular abnormalities such as intrahepatic portosystemic shunts, undetectable hepatocellular carcinomas, or liver metastases with low FDG uptake. Third, several clinical features between the study groups were inconsistent. There were significant differences in age, body weight, and FDG injection dose between patients with impaired renal function and those with normal renal function. These factors may have affected liver uptake. However, despite these limitations, this is the first report to note a significant increase in FDG uptake in both the liver and blood pool, which could be attributed to impaired renal function. The FDG uptake in the liver and blood pool may appear slightly higher in patients with impaired renal function; we confirmed that this trend existed. The increased FDG uptake in the liver or blood pool, which was generally used as the reference site for evaluating tumor uptake, could influence the assessment of therapeutic efficacy. As the number of patients with impaired renal function and the usefulness of PET/CT increase, it is important to understand and appropriately deal with various factors that affect PET images to avoid an inaccurate interpretation. Further studies are needed to confirm the adequacy of referencing to the liver and blood pool in patients with impaired renal function.

Conclusions

Increased liver uptake and mediastinal blood pool uptake on FDG PET/CT is associated with impaired renal function, which seems to be a factor associated with increased liver uptake and mediastinal blood pool uptake. Renal function (eGFR) was found to be significantly negatively correlated with both the liver and mediastinal blood pool uptake.

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Conflict of interest

The authors declare no competing interests.

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