

Variability in the amount of fluorine-18 fluorodeoxyglucose excreted in urine measured from oncology patients during PET/computed tomography imaging

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The objectives of this work were to estimate the amount of fluorine-18 fluorodeoxyglucose (¹⁸F-FDG) excreted (AFE) in the patient urine during the uptake phase as percentage of the injected activity and to examine the effect of blood glucose levels (BGL) on the excreted amount and whether it varies among men and women using statistical analysis methods. Radiation dose rates were measured at 1 m from 50 patients, 24 men and 26 women, before and after the first void using a calibrated ionization chamber. The ¹⁸F-FDG was injected in the patients using a calibrated automatic dose injection system. Statistical analysis using hypothesis testing was carried out. Patients with BGL above 5 mmol/l had a higher AFE of 12.3% in comparison with 8.3% of the patients with BGL below 5 mmol/l. A statistically nonsignificant correlation ($r = 0.183$, $P < 0.249$) between AFE and BGL was found; a nonsignificant difference was found in the AFE measured among the male and female patients. The AFE measured was $12 \pm 6\%$, with a range of

(2–30%). There was a wide variation in the first void time of 39 ± 8 min, with a range of (17–68) min. A simple noninvasive measurement method is presented that enabled the estimation of the amount of ¹⁸F-FDG excreted from the patient during voiding. Statistical analysis concluded that the amount of ¹⁸F-FDG excreted does not depend on sex, but is perhaps influenced by BGL. *Nucl Med Commun* 00:000–000 Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.

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Introduction

The amount of radioactivity released from the patient's body while voiding during the uptake phase and before scanning of the fluorine-18 fluorodeoxyglucose (¹⁸F-FDG)-PET imaging study affects the patient's safety primarily by lowering the bladder radiation dose. It also affects staff safety by lowering the radiation dose rate measured from patients and the quality of the imaging study by reducing any interference in tumor detection or potential artifacts because of the accumulation of radioactivity in the bladder over time. Therefore, the estimation of bladder voiding factor is of potential importance in radiation protection.

¹⁸F-FDG is a nonspecific tracer mainly used for metabolic activity and concentrates in metabolically active tumors and accumulates in areas with high metabolism such as the brain, heart, and active muscles. When ¹⁸F-FDG is injected into patients, the nonmetabolized ¹⁸F-FDG is eliminated from the body by glomerular filtration without being reabsorbed by the renal proximal tubules. Then, the eliminated ¹⁸F-FDG remains and accumulates in the bladder.

Voiding the bladder is recommended to patients by nuclear medicine staff and clearly mentioned in published international PET imaging clinical protocols as it will reduce a patient's bladder dose by eliminating the

unused activity of ¹⁸F-FDG by the patient body; prevent signal interference because of gamma emissions from the bladder; and reduce the exposure rate measured from the patient. Therefore, patients are asked to void at the end of the uptake time and before scanning.

Biological variability among individuals is the main reason for the measured variability in excreted levels of ¹⁸F-FDG and the literature shows results from North American and Japanese populations. A study from another population is therefore beneficial for the international scientific community; therefore, we have presented this local study as a sample of our oncology patients' population at large.

The first aim of this work was to calculate the amount of ¹⁸F-FDG excreted (AFE) presented as the percentage of the injected activity. The second aim was to determine whether there is a relationship between the AFE and the blood glucose levels (BGL) by examining the correlation between the two variables.

Materials and methods

Radiation dose rates were measured immediately before and after voiding to calculate AFE using Eq. (1) below. We have excluded from this analysis patients with measured dose rate after voiding that were slightly higher than before voiding because of some mild urine

Table 1 Patient data; there were 50 patients (24 men and 26 women) in this study

Parameter	Average	SD	Coefficient of variation (%)	Minimum	Maximum
Weight (kg)	76	27	36	15	171
BMI	29	9	31	11	58
Injected activity (MBq)	326	86	26	147	485
Time before voiding (min)	39	8	21	17	68
Excreted ^{18}F -FDG fraction (%)	12	6	50	2	30
Measured dose rate per unit activity ($\mu\text{Sv/h/GBq}$)	93.7	14	15	65	136
Blood glucose levels (mmol/l)	5.9	1.5	26	3.2	10.1

Coefficient of variation is the ratio of the SD over the average.

^{18}F -FDG, fluorine-18 fluorodeoxyglucose.

contamination on their clothes. The total number of patient measurements reported in this study is 50; details are shown in Table 1.

The radiation dose rate was measured using a calibrated ionization chamber (SmartIon Type: 2120 G; Thermo Franklin, Franklin, Massachusetts, USA). The ^{18}F -FDG dose was administered using an automatic dose injector (Intego; MedRad Inc., Indianola, Pennsylvania, USA). The injector is subject to quarterly quality assurance testing performed by the vendor's service engineer as per the manufacturer's recommendations to ensure the required accuracy in ^{18}F -FDG injected activity. The maximum error measured was 0.8% as per the last calibration report.

The measurements were performed at 1 m from the patient's body surface to the entrance of the ionization chamber-type radiation detector by marking the floor to show the exact standing positions to be able to reproduce the measurement geometry with ease and accuracy. The patient and the PET/computed tomography technologist performing the measurements were in standing positions and the radiation detector was aimed at the waist level of the patient. This work was approved by the hospital medical research ethics committee.

Measurement of excreted activity

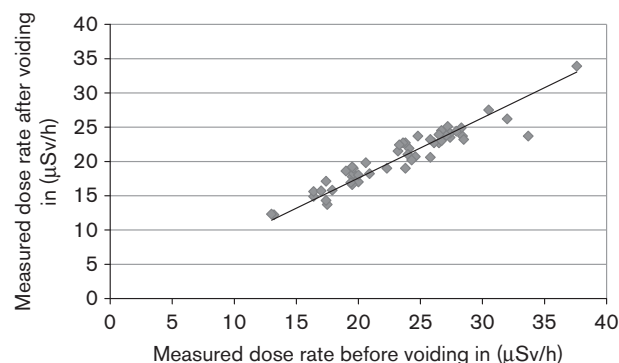
We have calculated the patient excreted amount of ^{18}F -FDG (AFE) as the difference between the measured dose rates at 1 m from the patient immediately before (D_{before}) and after voiding (D_{after}) over the dose rate measured before voiding (D_{before}) and presented as a percentage as Eq. (1) follows:

$$\text{AFE} = \left[\left(\frac{D_{\text{before}} - D_{\text{after}}}{D_{\text{before}}} \right) \right] \times 100 \%. \quad (1)$$

Statistical analysis

Both Lilliefors and Jarque–Bera hypothesis tests were used to test the hypothesis that both variables of patients' BGL and the excreted ^{18}F -FDG fraction fit to a normal distribution.

The two tailed Student *t*-test was used to test the hypothesis that there is no difference between the mean BGL of male and female patients. The test was also used

Fig. 1

Measured dose rate after voiding as a function of the dose rate before voiding.

to verify whether the EFP is different between the low BGL (below 5 mmol/l) and the high BGL (above 5 mmol/l) groups.

The correlation between the BGL and AFE was tested using the linear regression method and conclusions are reported. All the statistical analyses were carried out using MATLAB statistics toolbox (version 7.1) (Natick, Massachusetts, USA).

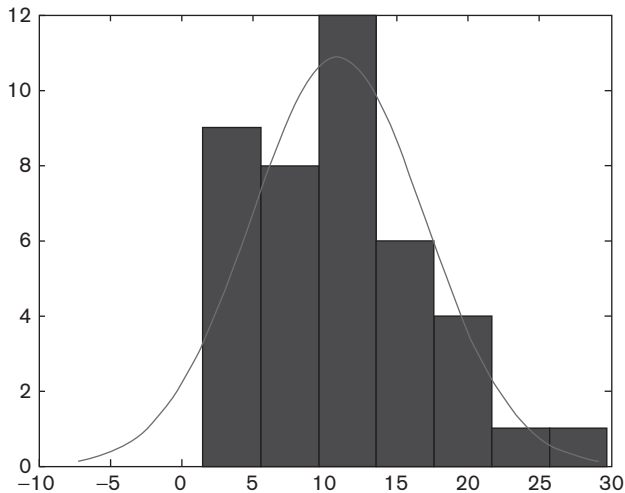
Results

The measured dose rates from the patients were reduced by $12 \pm 6\%$, with a range of (2–30%) because of voiding. We found a wide variation for the first void time; our average time measured before the first void was 39 ± 8 min, with a range of 17–68 min (Table 1). The ratio of the measured dose rates before and after voiding is shown in Fig. 1.

Statistical analysis

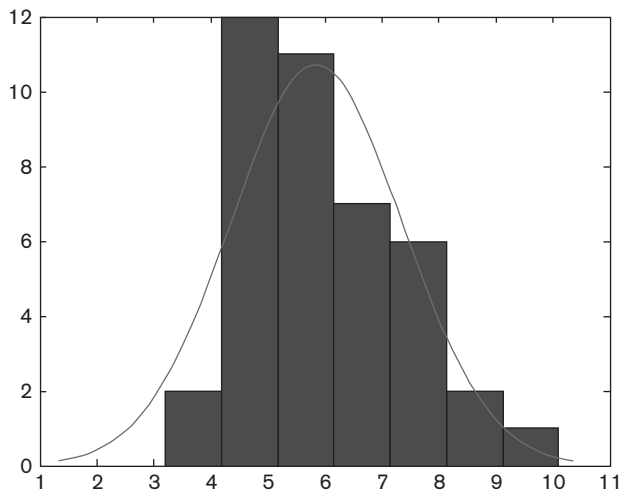
The patients' BGL and the excreted ^{18}F -FDG fraction variables were tested for goodness of fit to the normal distribution (Figs 2 and 3). The results indicated that both variables may come from a normal distribution and therefore the normality hypothesis cannot be rejected with ($P=0.078$ and 0.185) using the Lilliefors test and ($P=0.093$ and 0.048) using the Jarque–Bera test.

Fig. 2



Excreted ^{18}F -FDG fraction data frequency distribution with a superimposed normal distribution fit. ^{18}F -FDG, fluorine-18 fluorodeoxyglucose.

Fig. 3

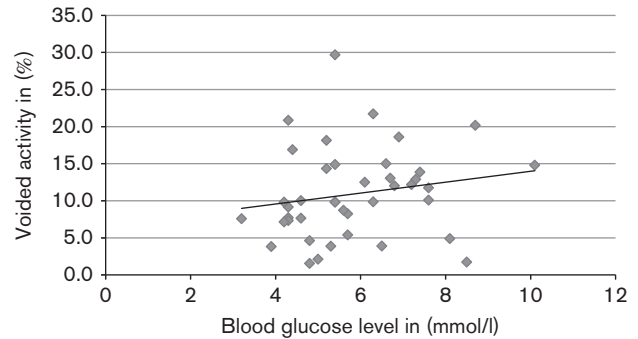


Blood glucose levels' data frequency distribution with a superimposed normal distribution fit.

The BGL distribution of both male ($n=24$, average level=6.2 mmol/l) and female ($n=26$, average level=5.5 mmol/l) patients was tested to determine whether there is a difference between the two subgroups using a Student t -test for the difference in means between two samples. The results indicated that the difference observed between the two groups is statistically nonsignificant ($P=0.141$).

However, we divided the patients' data according to the BGL into two groups: low-level group (below 5 mmol/l,

Fig. 4



Voided activity in (% of injected activity) as a function of the blood glucose level in (mmol/l) measured before activity administration.

$n=14$) and high-level group (above 5 mmol/l, $n=27$); the difference in the amount of excreted ^{18}F -FDG between the two groups was found to be statistically significant ($P=0.036$). The higher BGL group excreted 12.3% of the injected activity compared with 8.3% for the low BGL. This finding is important and warrants further investigations.

Finally, we found a statistically nonsignificant correlation between the BGL and ^{18}F -FDG fraction excreted ($r=0.184$, $P=0.249$) (Fig. 4).

The average excreted ^{18}F -FDG fractions for male and female patients were 11.9% and 10.0% of the injected ^{18}F -FDG activity, respectively. The results indicated that the difference observed between the two groups is statistically nonsignificant ($P=0.259$).

Discussion

Our results are in agreement with the study by Bach-Gansmo *et al.* [1]; they found urinary ^{18}F -FDG excretion to be highly variable, with a range of 5.7–15.2% of the injected dose using data from 20 patients undergoing PET/computed tomography imaging. In most cases, the patient will void before imaging, removing ~15–20% of the administered activity and thereby decreasing the dose rate by a factor of 0.85 [2].

The urinary excretion of ^{18}F -FDG prevented the distinction of the primary tumor from the surrounding tracer [3]; the feasibility of ^{18}F -FDG-PET imaging in patients with bladder cancer, despite a major remaining pitfall, is intense ^{18}F -FDG accumulation because of excretion in the urine [4].

Hays and Segall report that bladder radiation dose will be considerably reduced if the patient voids early after ^{18}F -FDG administration. They recommend that, when feasible, high fluid intake and early and frequent voiding after ^{18}F -FDG administration be encouraged [5]. The hydrated patients had a higher excretion of ^{18}F -FDG

than dehydrated patients, 16.98 versus 14.27%, and the volume of urine voided was significantly higher ($P < 0.020$); in contrast, the percentage of ^{18}F -FDG excreted in the urine appears to be independent of the volume of urine voided [6].

The amount of voided activity will contribute toward the dose reduction in the bladder of the patient. Jones *et al.* [7] reported a reduction in the order of 15% of the injected activity for the first 2 h after injection of the ^{18}F -FDG. Mejia *et al.* [8] reported a mean percentage of injected activity excreted to the bladder at 2 h void time of 21.2% and after 1 h to be around 13.3%.

The initial voiding time seems to play a role in the dose calculations to the bladder wall; the optimum initial voiding time to deliver the lowest dose according to the traditional MIRD static bladder model is 40 min [9]. Thomas *et al.* [10], using a dynamic bladder model, concluded that large initial bladder volumes and higher rates of urine flow into the bladder result in lower bladder wall dose. A study by Dowd *et al.* [11] on 302 adult patients over a 5-year period, indicates that when the bladder is large at the time of the injection, the dose to the bladder is markedly reduced and the optimal voiding time using the dynamic bladder model is 80 min.

Low radioactivity excretion in urine is an indication of good reabsorption by the kidneys [12]. It is known that increased glucose levels decrease ^{18}F -FDG uptake in the brain and in tumors because of direct competition between binding sites and enzymes [13]. A recent work carried out by Huang *et al.* [14] concluded that urinary excretion of ^{18}F -2FDG is significantly higher in the euglycemia than in the hyperglycemia condition in rats undergoing PET scanning by measuring urinary radioactivity concentration at 120 min after activity injection.

Generally, a number of studies in the literature have reported measured amounts of excreted ^{18}F -FDG in patients' urine. The reported measurement methods were most of the time invasive such as bladder catheterization [15] or time consuming because of urine collection and counting [1,7]. The simple method presented here using direct dose rate measurements has some advantages over the other methods in our opinion.

It is important to mention that P values calculated in the statistical analysis part of this study are strongly influenced by the sample size and by using a larger patient population, the difference between the two subgroups, women and men, will probably become statistically significant. Therefore, we recommend continuing collecting data to include a larger number of patients and re-examine the difference between the two groups again.

Conclusion

We have presented an absolutely noninvasive method to estimate the AFE in patient urine using dose rate measurements. The method is straightforward and can easily be reproduced in the clinical environment.

Patient bladder voiding before scanning reduced the measured dose rate at 1 m from the patient by about 12% for the patient population under study, which is agreement with other published studies.

We have found that patients with higher BGLs excreted larger ^{18}F -FDG proportions than those with lower BGLs; the ^{18}F -FDG proportion excreted was 12.3% for the higher BGL group compared with 8.3% for the lower BGL group. This conclusion is in agreement with Bach-Gansmo *et al.* [1], who reported that it is not improbable that the variation in urinary excretion of ^{18}F -FDG could be influenced by impaired glucose tolerance or reduced kidney function.

These conclusions are only preliminary and warrant a wider investigation including a larger number of patients to increase the sample size, which is known to directly affect the results of hypothesis testing in statistics.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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