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Uptake of 2-deoxy-2-[^{18}F]fluoro-D-glucose in the normal testis: Retrospective PET study and animal experiment

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Our retrospective PET and animal studies were conducted on a total of eight patients with normal testes and five male Sprague-Dawley rats. All the rats were necropsied at 60 minute post-injection of FDG, and the organs were removed and counted. The human testes were visualized on 60–70 minute FDG-PET images and whole- or partial-body images in all of the patients. The correlations between patient age over 50 years old and testis-to-muscle ratios, and patient age and SUVs were statistically significant, $r = -0.755$, $p < 10^{-6}$ ($n = 7$), $r = -0.900$, $p < 0.007$ ($n = 4$), respectively. FDG uptake of the rat testes was $0.162 \pm 0.004\%$ kg injected dose/g ($n = 5$). The uptake was approximately 6.0 and 3.6 times as high as muscle and blood levels, respectively. In conclusion, there is substantial uptake of FDG into the normal testis which declines with age. The normal levels of FDG uptake in the testis relative to the patient's age should be considered in the interpretation of FDG scans of the inguinal and lower pelvic regions.

Key words: testis, 2-deoxy-2-[^{18}F]fluoro-D-glucose, positron emission tomography

INTRODUCTION

TO DATE, 2-deoxy-2-[^{18}F]fluoro-D-glucose (FDG) has been one of the most clinically employed positron-emitting tracers by virtue of its utility in assessing glucose metabolism in a variety of tissues. Especially positron emission tomography (PET) with FDG is playing an important roles in detecting viable tumor tissues and monitoring the treatment response of various cancers.[1,2]

It is important to have a proper understanding of the exact biodistribution of FDG in normal subjects in the interpretation of FDG-PET imaging. It is well known that the normal *in vivo* distribution of FDG includes the brain, heart, kidneys and urinary tract at one hour after intravenous injection of the tracer.[1–3] Myocardial FDG uptake varies and is highly dependent upon the fasted or fed state of the patient. Skeletal muscle uptake of FDG may also vary and the muscle has increased accumulation of the tracer during or just after physical exercise.

To our knowledge, however, there are no reports on FDG uptake in the normal testis. In this report cases with FDG uptake in the normal testis are described and animal data are also given. Based on these results, the mechanism of testicular FDG uptake is discussed and inferred.

MATERIALS AND METHODS

Patient study

We retrospectively reviewed FDG-PET studies in our oncology section and studied reports on patients for whom the imaging included a testicular region. This study covered a total of eight patients, including 3 patients with bladder cancer, 3 with prostate cancer, 1 with both bladder and prostate cancers and 1 with melanoma. All of them underwent FDG-PET study in order to detect primary and metastatic lesions and/or to assess treatment response. The ages of the patients ranged from 39 to 77 years (average; 60.8 years).

Of the 4 patients with bladder cancer, 2 had undergone transurethral resection of a bladder tumor (TUR-BT), 1

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cystoprostatectomy and postoperative pelvic irradiation and 1 radical cystectomy plus chemotherapy prior to a FDG-PET study. Of the 4 patients with prostate cancer, 2 had undergone surgical biopsy and 2 radical prostatectomy (one, cystoprostatectomy) with postoperative pelvic irradiation prior to a FDG-PET study. None of the patients had been put on antihormonal therapy. One patient with radical prostatectomy with postoperative radiotherapy was completely impotent after the surgery.

Histopathologically-proven diagnoses were: 4 cases of transitional cell carcinoma of grade 3, 4 cases of adenocarcinoma of Gleason 5 to 8 and 1 of malignant melanoma. All had two normal testes, except one who had undergone a right orchiectomy for testicular atrophy following polio. In our series, neither swelling nor a tumor was noted in the testicular region.

Written informed consent was obtained from all of the patients after the study was explained to them in detail. All patients fasted for at least 4 hours before scanning. The serum glucose level was measured before scanning in all cases, and also after scanning in 4 cases. No patient was found to have a high glucose level or diabetes mellitus. We performed retrograde irrigation of the urinary bladder during the study in one patient, by inserting a double lumen Foley catheter (12F) and suspending a 1,000–3,000 m*l* bag of sterile saline for irrigation then draining the fluid to completely empty the bladder.

Imaging protocol

[^{18}F]fluoride was prepared with a medical cyclotron (T.C.C. model CS-30 cyclotron, Berkeley, Calif.) by accelerating deutrons into an $H_2{}^{18}O$ target.[4]

All patients were studied with a whole-body 8-ring (15 plane) positron emission scanner (Siemens CTI 931,921 PET scanner, approximately 10.3 cm, 15 cm. axial field view). The patients were supinely positioned head first in the scanner gantry with arms above the head so that the arms and head were through the scanner gantry. Transmission scans with a Ge-68 source were performed at the level believed to include the mass lesion. After the transmission images were obtained, the patient was positioned so that the scanner field (approximately 20 cm field of view) was at the imaging level believed to include the mass and the inguinal and testicular regions; then dynamic scan acquisition over 60 minutes was performed after intravenous injection of approximately 10 mCi of FDG (370 MBq).

At 60 to 70 minutes after the injection, the patients were repositioned and the second imaging levels were examined for 10 minutes. Post-void 60–70 minute images were taken in two patients. In addition, one patient had a "whole-body" FDG image, 15 minutes per image and one "partial-body" FDG image, 10 minutes per image, because of suspected multiple metastases to other remote organs. One patient underwent "whole-body" FDG images only.

PET images were reconstructed from projection data, and transaxial, coronal and sagittal sections were obtained with 15 contiguous slices with a slice thickness of 6.7 mm and a spatial resolution of 6.1 mm FWHM in the center of the field of view. All data were reconstructed in a 128 × 128 image matrix. The final inplane resolution in reconstructed and Hann-filtered images with 0.3 cut-off frequency was approximately 8 mm FWHM.

Image interpretation was performed on 60–70 minute transaxial images with or without post-voiding in 7 patients, and on the anterior "whole-body" image in one patient. Testis uptake was compared with that of the muscle and graded as follows: Testis uptake was classified into four grades: grade 0: no abnormal accumulation, grade 1: mild uptake, grade 2: moderate uptake and grade 3: intense uptake.

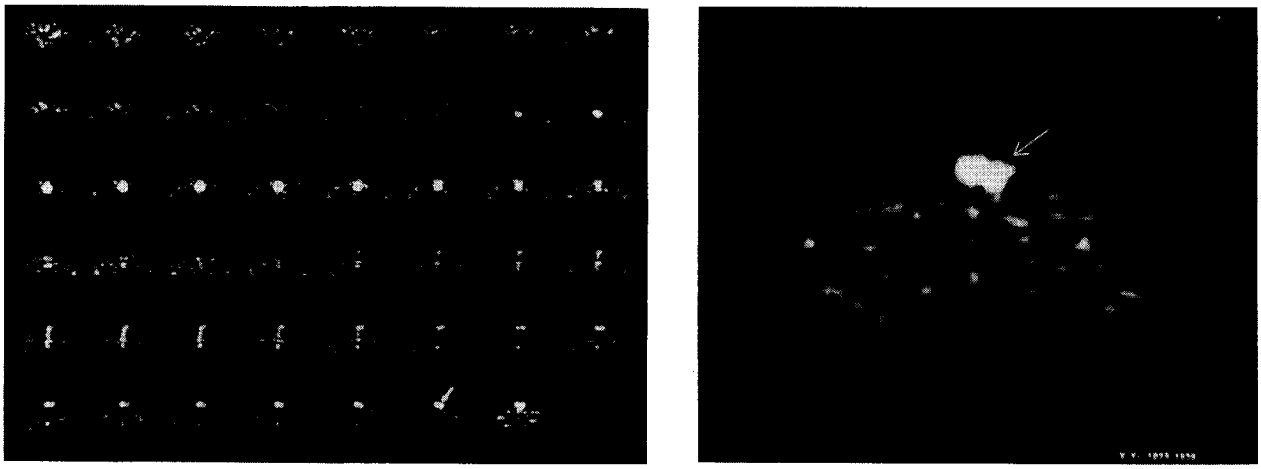
Testis uptake was quantitatively evaluated by means of the testis-to-muscle uptake ratio and/or standardized up-

Table 1 Standardized uptake values (SUVs) of the testes and testis-to-muscle uptake ratios

No.	Age	Sex	Disease	Therapy before study	Grading	SUV	Testis/Muscle
1	53	M	Prostate cancer		grade 3	rt: 2.92	rt: 3.84
						lt: 3.34	lt: 4.05
2	63	M	Prostate cancer	Right orchiectomy	grade 1		lt: 1.82
3	68	M	Prostate cancer	Prostatectomy & pelvic	grade 1	rt: 1.9	rt: 1.87
			Impotence	irradiation		lt: 1.9	lt: 1.9
4	68	M	Prostate cancer	Cystoprostatectomy &	grade 1	rt: 2.25	rt: 1.54
			Bladder cancer	pelvic irradiation		lt: 2.33	lt: 1.7
5	58	M	Bladder cancer	TUR	grade 2	2.45*	3.38*
6	60	M	Bladder cancer	TUR	grade 2		rt: 2.81
							lt: 2.58
7	39	M	Bladder cancer	Radical cystectomy & 3	grade 2		rt: 2.09
				cycles of chemotherapy**			lt: 1.81
8	77	M	Melanoma		grade 2		rt: 2.30
							lt: 2.05

*; The testis was not discernible as two probably due to overlapping each other

**; The combination of carboplatin and methotrexate



A B

Fig. 1 (A) FDG-PET transaxial sections of a 53-year-old male with the normal testes, sequentially from the lower pelvis to the inguinal region. Intense, focal FDG uptakes of two contiguous foci are noted between the legs in the lower two rows (arrow). There is urinary FDG in the bladder and penis, and mild FDG accumulation is noted in the rectum. (B) Magnified transverse FDG-PET image of the same patient. Note intense uptakes of FDG in the normal testes.

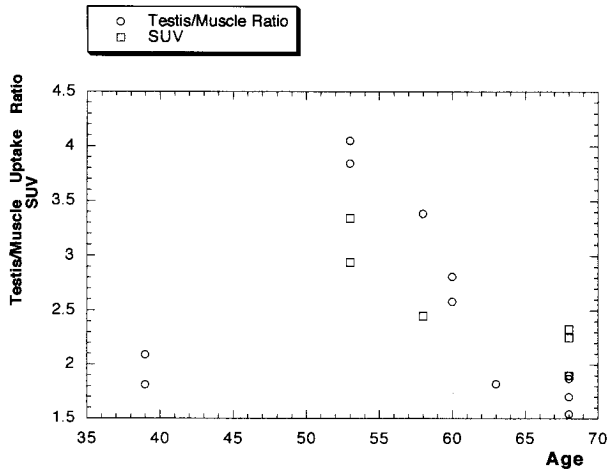


Fig. 2 Distribution of the testis-to-muscle uptake ratios and SUVs functioned by patient age.

take value (SUV) which was defined as follows:

SUV = decay-corrected dose/cc tumor/injected dose/patient weight (g).

SUV images were reconstructed in 4 patients from projection data obtained at 60–70 minutes post-injection, and SUVs were calculated from regions of interest (ROI) drawn on each testis. The ROIs were usually 12 pixels in size. SUV images were unavailable in the other 3 patients with transmission scan because of technical errors.

Animal study

Five male Sprague-Dawley rats, 397–490 g and 3.5 months of age (Charles River Breeding LABS, Wilmington, Mass.) were used. All rats were fasted overnight before the study. Four hundred micro curies (14.8 MBq) of FDG was injected into each rat via the femoral vein. The injection volume was 0.3 m*l*. All the rats were necropsied at 60 minutes post-injection of FDG.

The organs were removed and blotted to minimize adhering blood. The organs and urine samples obtained were weighed, counted and their biodistributions were calculated by standard methods. ^{18}F activity was counted in a Packard automated NaI gamma counter with a 511 keV window ± 20%. The activity was corrected for decay. Data were expressed as percentage kg of the injected dose per gram of tissue (% kg injected dose/g), which means % injected dose/gram normalized for a 1 kg animal.

RESULTS

Patient study

The testes were visualized on 60–70 minute FDG-PET images and whole- or partial-body images in all of the patients (Table 1). The testis uptake of FDG was clearly discernible because two round-shaped, solid, increased accumulations were present between the legs, corresponding to the site of the testes (Fig. 1). There was not a significant difference in visualization of testes in the same patient. Two patients, however, had one lumped accumulation probably due to overlapping in one patient (case No. 5) and orchiectomy in another patient (case No. 2). Grading of testicular accumulation was grade 3 (intense), 2 (moderate), and 1 (mild) for 1, 3 and 3 patients, respectively. SUVs ranged from 1.90 to 3.34 (average; 2.44 ± 0.53, n = 7), and the uptake ratios for testis-to-muscle were from 1.54 to 4.05 (average: 2.41 ± 0.81, n = 14). The younger the patients were, the higher the SUVs and the uptake ratios for testis-to-muscle were, if one case (case No. 7) is eliminated (Fig. 2). The correlations between patient age over 50 years and testis-to-muscle ratios, and

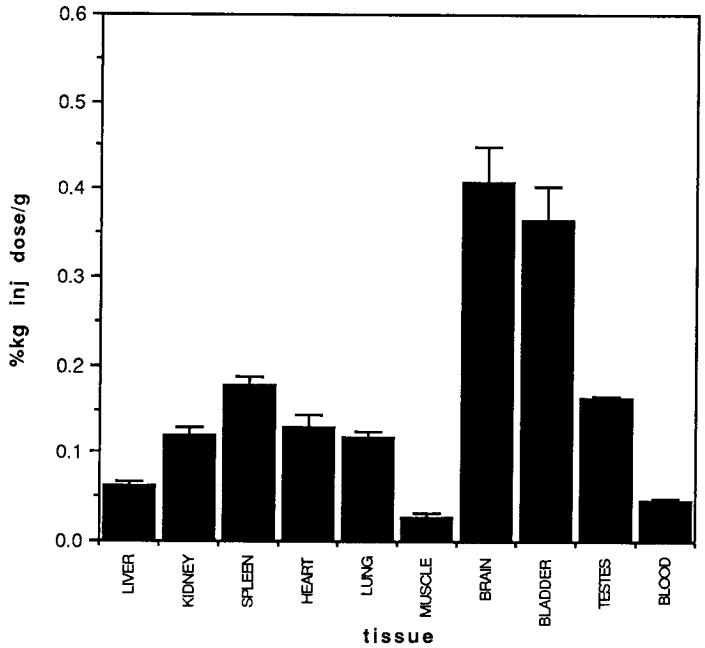


Fig. 3 FDG uptakes (% kg injected dose/gram) in normal rats organs (n = 5) at 60 min after iv injection of FDG. The high values of the bladder are probably due to contamination of urinary FDG.

patient age and SUVs were statistically significant, $r = -0.755$, $p < 10^{-6}$ ($n = 7$), $r = -0.900$, $p < 0.007$ ($n = 4$), respectively.

Animal study

Fig. 3 shows FDG uptakes (% kg injected dose/g) in the normal rat tissues one hour after the intravenous injection of FDG. Testis uptake of FDG was 0.162 ± 0.004% kg injected dose/g ($n = 5$). Testicular uptake of FDG was approximately 6.0 and 3.6 times as high as in muscle and blood, respectively.

DISCUSSION

It is important that the 'normal' pattern of FDG uptake be characterized and then used as a reference for interpreting studies of patients with malignant neoplasms. While glucose metabolism is found throughout the body, there are significant characteristics of FDG biodistribution in normal subjects.

Prominent accumulation of FDG in normal subjects is apparent in the brain, heart, kidneys and urinary tract.[1-3] The brain is physiologically known to account for approximately 20% of the total glucose metabolism of the body in the resting state.[5,6] Uptake of FDG in the heart and muscle is enhanced in the presence of insulin since the cell membranes have the action of glucose transporter, Glut4.[7,8] FDG uptake generally depends on plasma subtrate levels or the nutrition status of the patient, in viable tumor cells as well as the heart.[9]

FDG is rapidly excreted in the urine after iv injection. In canine studies urinary excretion of FDG is 16% and 50% of the injected dose at 60 and 135 minutes after the injection.[10] The lingual and palatine tonsils, and the floor of the mouth exhibit prominently increased FDG uptake,[11] but testis uptake of FDG is yet unknown in normal subjects despite the aforementioned, detailed observations.

In our series, all of the patients exhibited testicular uptake of FDG, with variable activity ranging from 1.90 to 3.34 in SUV. Five of 8 patients (62.5%) showed more than moderate accumulation of FDG in the testis. The patient population was small, but SUVs of the normal testis and testis-to-muscle uptake ratios were inversely well correlated with patient age with an r value of -0.755 for testis-to-muscle uptake ratio and -0.900 for SUV, if we eliminate one case (case 7). This case was very different from others in that the uptake ratios were calculated from the "whole-body" image which was not attenuation-corrected, and the patient had undergone intensive chemotherapy prior to the study.

Our male rat study also demonstrated that testis uptake of FDG was comparatively intense, with uptake approximately 6.0 and 3.6 times as high as muscle and blood uptake, respectively. The rats were 3.5 months of age, but testis uptake of FDG might have been mild or faint if an older male rat model had been employed.

The reason why the normal testis FDG uptake is greater in younger patients has not been elucidated. There is a positive correlation between SUV and body weight for blood, liver and spleen,[12] but our series showed testis-to-muscle uptake ratios inversely well correlated with patient age, and substantial testis uptake of FDG in the rat study. FDG uptake of the normal testis probably occurs

because steroidogenesis in the testis needs glucose uptake. Amrolia P, et al. showed that Leydig cells can take up 2-deoxy-D-[1,2-^{3}H]glucose by a transport system that appears to be similar to the facilitated-diffusion systems for glucose uptake, and that hexose uptake was significantly stimulated by luteinizing hormone (LH).[13] There is also a report that insulin wields an influence on biogenesis of testosterone in the testis.[14] In addition, it was recently reported that Glut5 exists in the human spermatozoa.[15] In an evaluation of FDG-PET in patients with breast cancer, an inverse correlation was seen between the normal breast FDG uptake and aging.[16] The higher glucose metabolism in the testis of young males might result in higher FDG uptake in the testes of younger patients. We should note the physiological testis uptake of FDG in the interpretation of PET scans, and the normal testis FDG uptake must not be misread as a pathological uptake.

In conclusion, there is some uptake of FDG into the normal testis which declines with age. The normal levels of FDG uptake in the testis relative to the patient's age should be considered in interpretating FDG scans of the inguinal and lower pelvic regions. Normal testis FDG uptake should not be confused with abnormal accumulation.

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