

Characterizing Normal Variant [⁶⁸Ga]Ga-FAPI-46 Uptake in the Epididymis

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The biodistribution of fibroblast activation protein inhibitor (FAPI) PET tracers includes the kidneys, bladder, uterus, breast, muscles, and bone marrow. We describe its occasional uptake patterns in the epididymis. **Methods:** Epididymal [⁶⁸Ga]Ga-FAPI-46 uptake was retrospectively analyzed in 55 PET/CT studies of 55 men. Uptake intensity (SUV), pattern (diffuse, focal, or multifocal), laterality, and location (epididymal head with or without body/tail) were analyzed. Electronic medical records were reviewed to determine the presence of epididymis-related disease. **Results:** Epididymal [⁶⁸Ga]Ga-FAPI-46 uptake was observed in 8 of 55 (15%) subjects, with bilateral epididymal head uptake in all cases and epididymal body/tail uptake in 6 of 8 (75%) cases, 5 of 6 (83%) bilaterally and 1 of 6 (17%) unilaterally. The average SUV_{max} was greater in the epididymal heads than in the epididymal bodies/tails, with an SUV_{max} of 4.1 versus 3.0 ($P < 0.001$). No subject had epididymal disease related to the uptake. **Conclusion:** [⁶⁸Ga]Ga-FAPI-46 uptake in the epididymis occurs occasionally and does not appear related to epididymal disease.

Key Words: FAPI; normal variant; epididymal head; epididymis; incidental

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Fibroblast activation protein (FAP) is a type II integral membrane glycoprotein enzyme, with functions relating to extracellular matrix remodeling and fibrogenesis. This protein is expressed by cancer-associated fibroblast subpopulations (CAF-S1 and CAF-S4) that may be present in more than 90% of epithelial cancers with a desmoplastic reaction (1–3). It is also expressed by the normal activated fibroblasts in inflammation and fibrosis but is not significantly expressed in healthy tissues (1,4,5).

FAP inhibitor (FAPI) radiopharmaceuticals have been developed to target FAP to investigate their potential in the diagnosis and treatment of multiple oncologic or nononcologic processes (4).

The normal biodistribution of FAPI PET tracers includes mainly the uterus, kidneys, bladder, and to a lower level the breast, muscles, and bone marrow (6,7). While analyzing [⁶⁸Ga]Ga-FAPI-46 PET/CT studies as part of multiple clinical trials, we identified occasional epididymal uptake. The goal of this study was to further characterize [⁶⁸Ga]Ga-FAPI-46 PET/CT uptake in the epididymis.

MATERIALS AND METHODS

We screened our database of 92 patients (56 men, 36 women) who underwent [⁶⁸Ga]Ga-FAPI-46 PET/CT in the clinical trials NCT04147494, NCT04457232, NCT04457258, NCT04459273, or NCT05365802 from December 18, 2019, to April 18 2023. The PET scans of all 56 male patients were retrospectively analyzed. The scans were acquired with a Siemens Biograph mCT scanner and a Siemens Biograph 64 TruePoint scanner. The CT scans were low-dose (120 keV, 30 mAs, slice thickness of 5 mm) and acquired without intravenous contrast medium. Uptake in the epididymides was evaluated in consensus by 2 nuclear medicine physicians. The epididymal structures were located on PET/CT by reviewing axial, coronal, and sagittal planes. Tracer uptake pattern (diffuse, focal, or multifocal), laterality, and location (epididymal head with or without body/tail) were noted. Uptake in the body or tail was recorded as being in the same structure (i.e., body/tail) as the body and tail could not be distinguished on PET/CT because of their small size. The SUV_{max} of the epididymal structures was collected by drawing 1-cm spheric volume of interests in the superior pole of the testes and in the region of most intense uptake in the epididymal bodies/tails. Blood pool SUV_{mean} was measured with a 1-cm spheric volume of interest in the descending thoracic aorta at the level of the carina. Epididymal SUV_{max}/blood pool SUV_{mean} ratios were calculated. We defined mild, moderate, and intense uptake as being ratios of 3 or less, 3–4, and more than 4, respectively. We reviewed the electronic medical records of all patients with any epididymal uptake to determine the presence of epididymis-related disease (e.g., epididymitis, epididymal tumor lesions, and epididymal cysts) by checking the past medical history and by searching the electronic medical record for the keyword *epididymis*. Paired *t* tests were performed using R software to assess the mean differences in uptake between the analyzed structures. The Shapiro–Wilk test was used to confirm no significant departure from normal distributions in the analyzed data. A Welch *t* test was performed using R to compare the age of the subjects with and without uptake in the epididymis.

The study was approved by the UCLA institutional review board (approval 22-001287), and the need for written informed consent was waived because of the retrospective design.

RESULTS

In total, the [⁶⁸Ga]Ga-FAPI-46 uptake in the epididymides of 55 of 56 men was analyzed. One PET/CT study was excluded because of poor image quality (excessive noise). The mean age of the population was 63 y (range, 24–85 y). The mean injected activity and time from injection to imaging were 181 MBq (range, 129–204 MBq) and 61 min (range, 47–100 min), respectively.

Of all subjects, 8 of 55 (15%) had uptake in their epididymides (Fig. 1). Of the 8 subjects with epididymal uptake, 8 of 8 (100%) had focal uptake in both epididymal heads (total, 16 epididymal heads), 6 of 8 (75%) had linear uptake in the epididymal bodies/tails, 5 of 6 (83%) had uptake bilaterally, and 1 of 6 (17%) had uptake unilaterally on the right (total, 11 epididymal bodies/tails).

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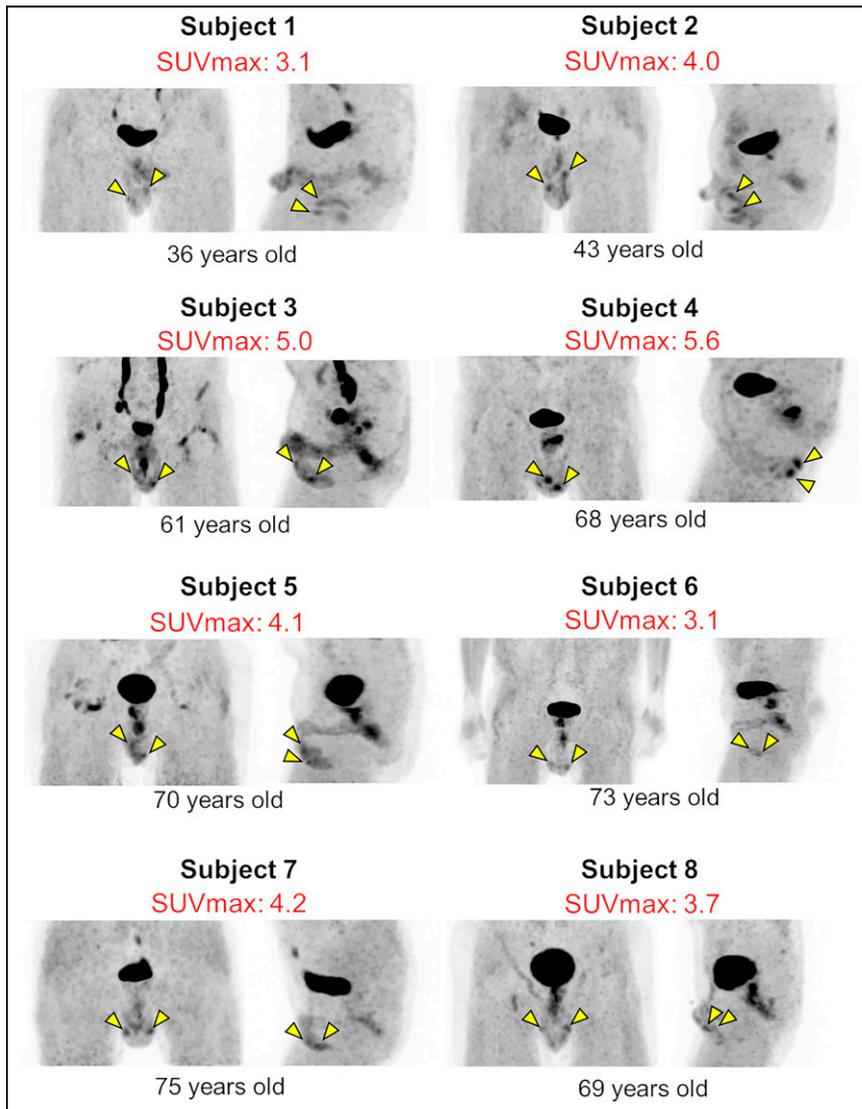


FIGURE 1. Maximum-intensity projection anterior (left) and lateral (right) images of all 8 subjects with epididymal [⁶⁸Ga]Ga-FAPI-46 uptake (arrowheads).

Table 1 describes the SUVs and signal-to-background ratios in all 8 subjects. Figures 2 and 3 and Supplemental Figures 1–3 illustrate examples of mild, moderate, and intense uptake in the epididymis (supplemental materials are available at <http://jnm.snmjournals.org>).

The uptake intensity in the epididymal heads ranged from mild to intense (7/16 [44%] mild, 4/16 [25%] moderate, and 5/16 [31%] intense), with a mean SUV_{max} of 3.9 (range, 2.6–5.6) and a mean SUV_{max}/SUV_{mean} blood pool ratio of 3.4 (range, 2.1–5.3).

The uptake intensity in the epididymal bodies/tails ranged from mild to moderate (9/11 [82%] mild and 2/11 [18%] moderate), with a mean SUV_{max} of 3.0 (range, 2.6–3.5) and a mean epididymal SUV_{max}/SUV_{mean} blood pool ratio of 2.7 (range, 2.0–3.3).

In subjects with uptake in both the epididymal heads and the epididymal bodies/tails, the mean SUV_{max} was greater in the heads (SUV_{max}, 4.1 vs. 3.0, $P < 0.001$, $n = 11$).

There was a small difference in the mean SUV_{max} between the right and left epididymal heads (3.7 vs. 4.1, respectively, $P = 0.040$, $n = 8$). There was no difference in the SUV_{max} between the right and left epididymal bodies/tails that had bilateral uptake (3.0 vs. 3.0, $P = 0.87$, $n = 5$).

There was no significant difference in the average age of the subjects between those with epididymal uptake (average, 62 y; range, 36–75 y) and those without (average, 63 y; range, 24–85 y) ($P = 0.82$). In these 8 patients with epididymal uptake, the median follow-up time after PET/CT was 4.8 mo (range, 1–28 mo). Two subjects

TABLE 1
Epididymal [⁶⁸Ga]Ga-FAPI-46 SUVs and Signal-to-Background Ratios

Subject no.	Epididymal head (R)		Epididymal head (L)		Epididymal body/tail (R)		Epididymal body/tail (L)	
	SUV _{max}	SUV _{max} /BP SUV _{mean}	SUV _{max}	SUV _{max} /BP SUV _{mean}	SUV _{max}	SUV _{max} /BP SUV _{mean}	SUV _{max}	SUV _{max} /BP SUV _{mean}
1	3.1	3.1	3.0	3.0	2.7	2.7	2.8	2.8
2	4.0	3.6	4.0	3.6	2.8	2.5	3.2	2.9
3	4.1	3.4	5.0	4.2	3.4	2.8	3.3	2.8
4	5.6	5.3	5.6	5.3	3.5	3.3	3.2	3.0
5	3.9	2.1	4.1	2.2	None	None	None	None
6	2.6	2.2	3.1	2.6	None	None	None	None
7	3.7	4.1	4.2	4.7	2.7	3.0	None	None
8	2.8	2.2	3.7	2.8	2.6	2.0	2.6	2.0

BP = blood pool; none = no uptake above background.

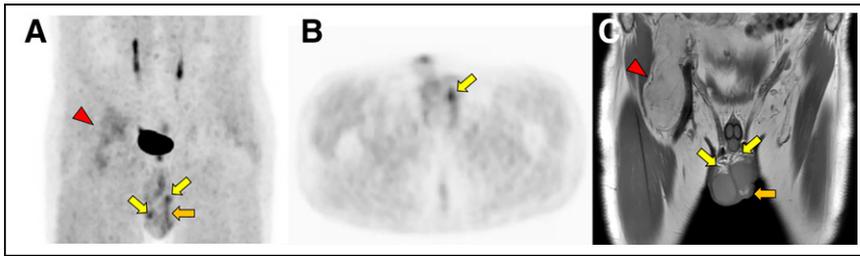


FIGURE 2. Subject 2 (43-y-old man) from Table 1. Shown are [^{68}Ga]Ga-FAPI-46 maximum-intensity projection coronal PET (A), axial PET (B), and coronal T1-weighted MR images (C). Moderate uptake is demonstrated bilaterally in epididymal heads (yellow arrows). Mild uptake is demonstrated in left epididymal body/tail (orange arrows). There was mild uptake in right epididymal body/tail (not shown). Epididymal tissue was demonstrated on MRI, with no epididymal disease reported. Biopsy-proven hibernoma with mild uptake was noted (arrowheads).

had less than 3 mo of follow-up (31 and 55 d), and 6 of 8 had more than 3 mo of follow-up.

On follow-up, no subject had known clinical epididymal disease related to [^{68}Ga]Ga-FAPI-46 uptake. One subject (subject 8, Fig. 1 and Table 1) had a documented left epididymal cyst diagnosed on ultrasound 5 mo before undergoing [^{68}Ga]Ga-FAPI-46 PET/CT. However, this subject had uptake in both epididymal heads and bodies/tails, making this pathology unlikely the cause of the uptake.

DISCUSSION

The epididymis, a tightly coiled structure divided into a head, body, and tail, spans from the upper testicular pole to the lower testicular pole and can reach 6 m in length when uncoiled (8). The largest part of the epididymis is its head, with its thickness typically measuring 10–12 mm in the anteroposterior dimension. The body and tail are smaller, with the body having an average thickness of 1–2 mm (9). The epididymis has multiple functions regarding sperm maturation, storage, and transport (10).

During our [^{68}Ga]Ga-FAPI-46 PET trials, we noticed occasional epididymal uptake in our [^{68}Ga]Ga-FAPI-46 cohort, and the goal of this analysis was to formally assess this uptake. We were able to retrospectively identify uptake in the epididymis in a minority of our study population (8/55, 15%).

None of these 8 patients had known epididymal disease. Epididymal uptake was always present bilaterally in the head, most often mild and slightly more prominent on the left, with associated less intense unilateral or bilateral uptake in the body/tail.

epididymal hyperemia.

Uptake patterns in the epididymal head have also been described with [^{18}F]piflufolostat, [^{68}Ga]Ga-DOTANOC, and [^{177}Lu]Lu-DOTA-TATE, potentially explained by prostate-specific membrane antigen and somatostatin receptor expression in inflammatory cells such as macrophages (14–17). No association between age and [^{68}Ga]Ga-FAPI-46 uptake in the epididymis was found in our study. Because our study population was small, other potential clinical factors potentially influencing epididymal [^{68}Ga]Ga-FAPI-46 uptake were not evaluated. Further larger prospective studies are warranted.

As a main limitation of the study, there was no histopathologic validation of the observed PET signal. The focal uptake in the upper pole of the testes was presumed located in the epididymal head because it is the only focal structure in that region and because adjacent blood pool uptake is unlikely since [^{68}Ga]Ga-FAPI-46 signal in the blood pool is minimal. Linear uptake inferior to the epididymal head was presumed located in the epididymal body/tail as it is the only structure that could have this uptake pattern: it would be unusual for only a portion of the tunica vaginalis to express FAP. The systematically observed greater uptake in the epididymal head than in the body/tail can be in part explained by the size difference in the structures, leading to a greater partial-volume effect in the smaller epididymal body/tail. The study population was small, and other potential clinical factors potentially influencing epididymal [^{68}Ga]Ga-FAPI-46 uptake were therefore not evaluated. Further larger prospective studies are warranted.



FIGURE 3. Subject 4 (68-y-old man) from Table 1. Shown are [^{68}Ga]Ga-FAPI-46 PET maximum-intensity projection coronal PET (A), CT (B), and PET/CT (C) images. Intense uptake is demonstrated bilaterally in epididymal heads (yellow arrows). Moderate uptake is demonstrated in epididymal bodies/tails (orange arrows). Intense uptake is demonstrated in site of treated anal abscess (arrowheads).

FAP and FAP RNA expression in the epididymis has been observed on histopathology (11). In the Human Protein Atlas, FAP expression in the epididymis and testes has been quantified as moderate by immunohistochemical staining patterns. FAP RNA expression in the epididymis has been quantified as greater than in the testes (by normalized transcripts per million) (12).

The exact cause of occasional [^{68}Ga]Ga-FAPI-46 uptake in the epididymis is unclear but suggests the presence of occasional fibrosis and inflammation, which is supported by the known presence of inflammatory cells and fibroblast growth factor receptors in the epididymis (13). This uptake may also reflect

CONCLUSION

To our knowledge, this is the first reported study describing epididymal [^{68}Ga]Ga-FAPI-46 uptake patterns. Although the exact cause of this uptake remains unknown, it is important to avoid unnecessary additional investigations by being aware that occasionally there is [^{68}Ga]Ga-FAPI-46 uptake in the epididymis unrelated to known clinically manifested epididymal disease. To define the true incidence of FAP expression in the epididymis, larger study populations are needed.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

KEY POINTS

QUESTION: What are the [⁶⁸Ga]Ga-FAPI-46 epididymal uptake characteristics on PET/CT?

PERTINENT FINDINGS: Fifteen percent of our study population had epididymal uptake unrelated to epididymal disease.

IMPLICATIONS FOR PATIENT CARE: While interpreting [⁶⁸Ga]Ga-FAPI-46 PET/CT studies, readers should be aware that occasional epididymal uptake unrelated to known epididymal disease can be seen.

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