Characterizing Normal Variant $[^{68}\text{Ga}]$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 $[^{68}\text{Ga}]	ext{Ga}$-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 $[^{68}\text{Ga}]	ext{Ga}$-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$_{\text{max}}$ was greater in the epididymal heads than in the epididymal bodies/tails, with an SUV$_{\text{max}}$ of 4.1 versus 3.0 ($P < 0.001$). No subject had epididymal disease related to the uptake. **Conclusion:** $[^{68}\text{Ga}]	ext{Ga}$-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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**F**ibroblast 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 ($I$–$3$). It is also expressed by the normal activated fibroblasts in inflammation and fibrosis but is not significantly expressed in healthy tissues ($I$, $4$, $5$).

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 $[^{68}\text{Ga}]	ext{Ga}$-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 $[^{68}\text{Ga}]	ext{Ga}$-FAPI-46 PET/CT uptake in the epididymis.

**MATERIALS AND METHODS**

We screened our database of 92 patients (56 men, 36 women) who underwent $[^{68}\text{Ga}]	ext{Ga}$-FAPI-46 PET/CT in the clinical trials NCT04147494, NCT04457232, NCT04547258, 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 mA/s, 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 epididymides and the normal variants were identified on the PET/CT images. The epididymides were defined as having uptake in the epididymal heads/tails by reviewing the entire image set of the patient and by searching the electronic medical record for the keyword epididymis.

**RESULTS**

Of all subjects, 8 of 55 (15%) had uptake in their 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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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\textsubscript{max} of 3.9 (range, 2.6–5.6) and a mean SUV\textsubscript{max}/SUV\textsubscript{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\textsubscript{max} of 3.0 (range, 2.6–3.5) and a mean epididymal SUV\textsubscript{max}/SUV\textsubscript{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\textsubscript{max} was greater in the heads (SUV\textsubscript{max}, 4.1 vs. 3.0, \(P < 0.001, n = 11\)). There was a small difference in the mean SUV\textsubscript{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\textsubscript{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

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### Table 1

<table>
<thead>
<tr>
<th>Subject no.</th>
<th>Epididymal head (R)</th>
<th>Epididymal head (L)</th>
<th>Epididymal body/tail (R)</th>
<th>Epididymal body/tail (L)</th>
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<tbody>
<tr>
<td></td>
<td>SUV\textsubscript{max}</td>
<td>SUV\textsubscript{max}/BP</td>
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<td>SUV\textsubscript{max}</td>
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</table>

BP = blood pool; none = no uptake above background.
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 [68Ga]Ga-FAPI-46 PET trials, we noticed occasional epididymal uptake in our [68Ga]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.

Consequently, because epididymal uptake was always present in the head, we concluded that epididymal uptake was unlikely due to adjacent blood pool uptake (11). In our study, epididymal uptake was always present bilaterally in the head, most often mild and found in 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).

CONCLUSION

To our knowledge, this is the first reported study describing epididymal [68Ga]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 [68Ga]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 $^{68}$GaGa-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 $^{68}$GaGa-FAPI-46 PET/CT studies, readers should be aware that occasional epididymal uptake unrelated to known epididymal disease can be seen.

REFERENCES