Value of [68Ga]Ga-FAPI-04 Imaging in the Diagnosis of Renal Fibrosis

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Abstract

Purpose

Renal fibrosis is a pathological state in the progression of chronic kidney disease. Early detection and treatment are vital to prolong the survival of patients. Renal puncture examination represents the gold standard examination method for renal fibrosis, but it has several limitations. This study aims to evaluate the diagnostic performance of a novel PET radiotracer, [^{68}Ga]Ga-fibroblast activation protein inhibitor (FAPI)-04, which specifically images fibroblast activation protein (FAP) expression for renal fibrosis.

Methods

All patients underwent renal puncture before receiving [^{68}Ga]Ga-FAPI-04 PET/CT imaging. They then underwent [^{68}Ga]Ga-FAPI-04 PET/CT and immunochemistry examinations, and the data obtained were analyzed.

Results

The [^{68}Ga]Ga-FAPI-04 PET/CT examination results showed that almost all patients (12/13) exhibited increased radiotracer uptake. The maximum standardized uptake value (SUVmax) in patients with mild, moderate, and severe fibrosis was 3.92 ± 1.50 , 5.98 ± 1.6 , and 7.67 ± 2.23 , respectively.

Conclusion

Compared with renal puncture examination, non-invasive imaging of FAP expression through [^{68}Ga]Ga-FAPI-04 PET/CT can quickly show the patient's bilateral kidney condition with high sensitivity. This can facilitate the evaluation of the patient's disease progression, diagnosis, and the development of a treatment plan.

Introduction

Renal fibrosis refers to the pathological changes caused by the deposition of extracellular matrix in the kidney, including glomerulosclerosis, renal interstitial fibrosis, and arteriosclerosis [1, 2]. It does not refer to a specific disease but to a pathological state in the progression of almost all chronic kidney diseases (CKDs), which often indicates an irreversible decline in renal function. Renal fibrosis is closely related to patient prognosis. As renal fibrosis progresses, functional nephrons gradually decrease, and it eventually progresses to end-stage renal disease (ESRD) [3, 4]. Due to a lack of reliable, easy renal fibrosis assessment methods, it is difficult to precisely determine its prevalence. However, given the 10.8% prevalence of CKD, it can be inferred that There are a large number of patients with renal fibrosis [5].

There is a growing body of renal fibrosis research. At present, many factors are believed to affect renal fibrosis, including myofibroblasts, many cytokines, such as TGF- β , transcription factors, macrophages, and autophagy. The proposal of partial epithelial-mesenchymal transition (pMET) deepens our

understanding of renal fibrosis [6-11]. An accurate assessment of the degree of renal fibrosis is important to patients' diagnosis, treatment, and efficacy judgment.

The origin of cancer-associated fibroblasts (CAFs) is hypothesized to include the activation of resting tissue fibroblasts, the transdifferentiation of stromal cells or epithelial cells, the recruitment of circulating mesenchymal stem cells, or the differentiation of tissue-resident stem cells [12]. The hallmark of CAFs is the absence of FAP in normal human tissues that overexpress FAP on the cell surface. The radiolabeled FAP inhibitor [^{68}Ga]Ga-FAPI-04 was developed as a radiotracer for PET/CT imaging. At present, the clinical value of [^{68}Ga]Ga-FAPIs PET/CT for renal fibrosis has not been systematically studied. The purpose of this research is to improve the detection rate of renal fibrosis through non-invasive imaging technology and facilitate the clinical diagnosis and treatment.

Patients, Materials And Methods

Patients

A total of 13 patients were enrolled in the study. These patients had undergone renal puncture at the Affiliated Hospital of Southwest Medical University between January of 2020 and October of 2020 due to their condition. Hematoxylin-eosin (HE) and Periodic Acid-Schiff (PAS) staining showed that the patients' kidneys had varying degrees of renal fibrosis. The study excluded all patients with general health conditions affecting cardiopulmonary function/mental status and allergies to alcohol. This study was approved by the Ethics Committee of the First Affiliated Hospital of Southwest Medical University and followed the 1964 Helsinki Declaration and its subsequent amendments to the ethical standards. All patients signed written informed consent forms. [^{68}Ga]Ga-FAPI-04 was provided based on compassionate use. All patients underwent PET/CT examinations, and immunochemical examinations were performed on the kidney tissues collected before the patients were enrolled in the study (see Table 1 for patients' information).

The average age of the patients was 42.0 ± 17.0 (18–69 years). All patients showed pathological findings (HE and PAS staining) of renal interstitial fibrosis. Five patients had mild fibrosis, five had moderate fibrosis, and three had severe fibrosis. The evaluation parameters (including glomerulosclerosis, renal tubular atrophy, interstitial inflammation, and fibrosis) corresponded to three grades of I, II, and III, respectively, equivalent to affected proportions of < 25%, 25–50%, >50%.

Imaging and image analysis

Imaging was performed after the patient was in the Department of Nephrology, Affiliated Hospital of Southwest Medical University. Each patient provided a detailed medical history and underwent a physical examination before imaging. The dose of intravenous radiotracer was 0.05–0.07 mCi/Kg, and imaging was performed 50–60 min after radiotracer injection. All patients were required to urinate as much as possible to prepare for imaging. Urination reduces the influence of the residual radiotracer in the renal pelvis and calyces. Some patients with poor renal function were given diuretics. For the whole-body

inspection, the scope was from the base of the skull to the base of the thigh, using five to six beds (three min/bed). The matrix was 128×128, the PET layer thickness was 3 mm, and all PET images were reconstructed iteratively. All of the above inspection procedures were communicated to patients before obtaining written informed consent.

The image interpretation of [⁶⁸Ga]Ga-FAPI-04 PET/CT was based on visual and semi-directional analysis and was evaluated by two experienced nuclear medicine doctors. The mean standardized uptake value (SUVmean) of a round sphere with a diameter of 2 cm was selected from the liver as the kidney background, and the SUVmax of the kidney lesions was divided by the SUVmean in non-lesion tissues to calculate the target background ratio (TBR). Nuclear medicine physicians and nephrology physicians checked the patient's general condition (mental state/blood pressure/heart-rate/body temperature) until 120 min after radiotracer injection and were required to report any abnormalities.

Immunohistochemistry

The kidney tissue was stained by an antibody against fibroblast activation protein-α (FAPα), treated with formalin, and then embedded in paraffin. All kidney tissues were obtained from the archives of the Department of Pathology, Affiliated Hospital of Southwest Medical University. The immunohistochemical image was evaluated by the scoring system adopted by Henry et al. in which kidney tissue is evaluated as 0 (no FAP immunostaining), 1+ (<10% of stromal cells showing positive FAP staining), 2+ (10–50% of stromal cells showing positive FAP staining), and 3+ (>50% of stromal cells showing positive FAP staining).

Statistical Analysis

SPSS software (version 26.0; IBM, Armonk, NY) was used for statistical evaluation, and Graphpad8.0 was used for graphing. Measurement data were expressed as mean ± standard deviation. A one-way analysis of variance (ANOVA) was used to compare the different degrees of renal fibrosis between groups. The Kruskal-Wallis non-parametric rank-sum test was used for the groups that did not meet the parameter test conditions. $P \leq 0.05$ indicated statistical significance.

Results

Diagnostic Performance of [⁶⁸Ga]Ga-FAPI-04 PET/CT in Primary Tumors

In this study, increased radiotracer uptake was detected in most patients (12/13). As the patients' HE and PAS staining showed that the degree of renal fibrosis gradually increased, patients' SUVmax, serum creatinine (Scr), and TBR gradually increased and their glomerular filtration rate (GFR) gradually decreased. The patient indicators for different grades of renal fibrosis were compared with the mean±standard deviation. The SUVmax of patients with renal fibrosis grade Ⅱ (3.92±1.50) was statistically significantly lower than that of patients with renal fibrosis grade Ⅲ (7.67±2.23) ($P < 0.05$). However, the difference in SUVmax between patients classified as Ⅱ and those classified as Ⅱ and Ⅲ was

not statistically significant ($P > 0.05$). Similar results appeared in the patients' TBR and GRF data. There was a statistical difference between patients with renal fibrosis grades Ⅲ and Ⅳ, while there was no statistical difference between the data of patients with renal fibrosis grade Ⅲ and those of patients with grades Ⅱ and Ⅲ. The Scr of patients with renal fibrosis grade Ⅲ (3.92 ± 1.50) and the Scr of patients with grade Ⅱ (160.28 ± 66.39) were statistically significantly lower than those of patients with renal fibrosis grade Ⅳ (465.27 ± 274.72) ($P < 0.05$). However, the difference in Scr between patients with grade Ⅲ and patients with grade Ⅱ was not statistically significant. Figures 1–4 show the examination images of some of the patients, and Tables 2 and 3 and Figure 5 show the statistical results of the study.

Immunohistochemistry

Through immunohistochemical staining of antibodies specific for FAP α , FAP expression in renal interstitial cells was found in 10 patients (76.9%), and FAP expression in glomerular cells was found in four patients (30.7%). Figures 1–4 (g, h) show examples of FAP expression in renal fibrosis detected by immunohistochemistry.

Secondary primary imaging results

A diffusely increased intake of radiotracer in the breast (SUVmax was 11.7) was found in one young female patient, which may have been related to the patient's dense glands or changes in hormone levels [13, 14]. Two patients' psoas major muscles also increased radiotracer intake. After the two patients were questioned, we realized they engaged in agriculture and bus driver occupations, which may have damaged their lumbar muscles. The psoas muscle disease of the two patients was diagnosed as lumbar muscle strain.

Adverse events

All patients tolerated [^{68}Ga]Ga-FAPI-04 PET/CT examination well. There were no signs of drug-related pharmacological effects or physiological reactions. All patients' vital signs (blood pressure/heart-rate/body temperature) were kept within the normal range during, before, and after the examination. No patients reported any abnormalities.

Discussion

To date, no serological indicators have been found that can specifically reflect the degree of renal fibrosis. Blood lysyl oxidase (LOX), human epididymis protein 4 (HE4), and pentraxin-2, have the potential to assess renal fibrosis, but they are easily affected by other fibrotic diseases (liver fibrosis, pulmonary fibrosis, etc.) [15–17]. Non-invasive imaging examinations such as B-ultrasound can only indirectly reflect renal fibrosis through renal anatomical changes, making it difficult to determine the degree of renal fibrosis early and accurately. Due to the potential impact of contrast agents on renal function, enhanced CT is also unsuitable for evaluating renal fibrosis, especially for ESRD patients. The current imaging methods for assessing the degree of renal fibrosis have some limitations [18].

At present, the main method to accurately assess the presence and severity of renal fibrosis is kidney tissue biopsy. Although it is reliable, it has some contraindications and may cause corresponding complications, which hinders its wide clinical application. In addition, it can only reflect the fibrosis of the kidney tissue at the puncture site and not the degree of fibrosis as a whole[19]. Therefore, it is vital to find other non-invasive methods with better specificity and sensitivity to accurately assess the degree of renal fibrosis.

In this study, [^{68}Ga]Ga-FAPI-04 was used to detect renal fibrosis. It proved to be a promising new imaging method. Higher uptake of radiotracer was found in almost all patients (12/13). Because of the high average values of TBR and SUVmax, it was easier to distinguish the radiotracer with higher uptake of renal parenchyma from the background. The SUVmax and TBR of most patients correlated with the pathology of kidney tissue. [^{68}Ga]Ga-FAPIs PET/CT examination may enable diagnosis of renal fibrosis without a biopsy. You can instruct the kidney biopsy site for patients with focal renal fibrosis. [^{68}Ga]Ga-FAPIs PET/CT can also detect early renal fibrosis.

This study has some limitations, including the fact that a small number of patients (2/13) still had some residual radiotracer in the renal pelvis and calyces, which may have affected image quality. Also, the small number of patients included in the study and the uneven number of patients with various types of renal fibrosis limited the statistical significance. In the future, a larger patient cohort is needed to study the value of [^{68}Ga]Ga-FAPI PET/CT in renal fibrosis. In summary, compared with traditional renal puncture examinations, [^{68}Ga]Ga-FAPIs PET/CT can quickly show the histology of renal fibrosis. In patients for whom renal puncture is unsuitable, [^{68}Ga]Ga-FAPIs PET/CT scans can be used to help make rapid and effective treatment plans to improve patients' treatment results.

In recent years, research on [^{68}Ga]Ga-FAPIs in benign lesions has been progressing rapidly. Increased FAP has reportedly been found in refractory rheumatoid arthritis[20]. Besides renal fibrosis, high intake of FAPI has been found in benign diseases such as liver fibrosis, arthritis, cardiovascular disease, Crohn's bowel disease, idiopathic retroperitoneal fibrosis, pancreatitis, and osteophytes [21-28]. The diagnostic utility of [^{68}Ga]Ga-FAPIs needs further exploration.

Conclusion

The results of this preliminary study indicate that radiolabeled FAPI imaging can be used to image renal fibrosis. The imaging quality of [^{68}Ga]Ga-FAPI-04 PET/CT scans in patients with moderate-to-severe renal fibrosis may be superior, but more clinical trials are needed for further evaluation.

Declarations

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval All procedures involving human participants were performed in accordance with the ethical standards of the institutional committee, as well as the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This article does not contain any animal experiments.

Consent to participate Informed consent was obtained from all participants included in the study.

Consent for publication Informed consent was obtained from all participants included in the study.

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Tables

Due to technical limitations, table 1, 2 and 3 is only available as a download in the Supplemental Files section.

Figures

Figure 1

A 58-year-old man experienced decreased urine output and proteinuria for six months and lower limb edema for three months. The maximum intensity projection (MIP) image of whole-body [68Ga]Ga-FAPI-04 PET (a) shows diffuse uptake of radiotracer in both kidneys. The cross-sectional images (b–d) show moderate radiotracer uptake in both kidney parenchyma, and the SUVmax was 5.71, suggesting diffuse fibrosis of the kidneys. The pathological examination led to a diagnosis of membranoproliferative glomerulonephritis (severe renal interstitial fibrosis). HE and PAS staining (e, f) supported this diagnosis. The immunochemical examination (g, h) found FAP in both the glomeruli and renal interstitium. The pathological results are consistent with the PET/CT examination results.

Figure 2

A 56-year-old woman presented with edema and proteinuria with no obvious cause. The maximum intensity projection (MIP) image of whole-body $[^{68}\text{Ga}]\text{Ga-GAPI-04}$ PET (a) shows diffuse uptake of radiotracer in both kidneys. The cross-sectional images (b–d) show that the kidney parenchyma had slight radiotracer uptake and the SUVmax was 4.4, suggesting diffuse fibrosis of both kidneys. The pathological examination led to a diagnosis of minimal change glomerulonephritis (moderate fibrosis of renal interstitium). HE and PAS staining (e, f) supported this diagnosis. The immunochemical examination (g, h) found FAP in the renal interstitium, while no FAP was found in the globular tissue. The pathological results were consistent with the results of PET/CT. In this case, it was found that the patient's bilateral psoas muscle radiotracer intake was slightly increased, and the SUVmax was 3.0. Upon questioning, we found that the patient had a long-term occupational history of manual agriculture. Finally, the patient's lumbar muscle disease was diagnosed as lumbar muscle strain.

Figure 3

A 30-year-old man presented with edema of his lower limbs and face for more than four months, with foamy urine and pleural effusion. The maximum intensity projection (MIP) image of whole-body $[^{68}\text{Ga}]\text{Ga-FAPI-04}$ PET (a) shows diffuse uptake of radiotracer in both kidneys. The cross-sectional images (b–d) show heavy radiotracer uptake in both kidney parenchyma, and the SUVmax was 8.18, suggesting diffuse fibrosis of the kidneys. The pathological examination led to a diagnosis of crescentic glomerulonephritis (glomerular and renal interstitial mild fibrosis), and HE and PAS staining (e, f) supported this diagnosis. The immunochemical examination (g, h) found FAP in the glomerulus, but almost no FAP was found in the renal interstitium. The pathological results were consistent with the results of PET/CT.

Figure 4

A 25-year-old man had decreased renal function and proteinuria during a physical examination more than three months ago. The maximum intensity projection (MIP) image of whole-body [68Ga]Ga-FAPI-04 PET (a) shows diffuse radiotracer uptake in both kidneys. The cross-sectional images (b–d) show light radiotracer uptake in both kidney parenchyma and SUVmax was 7.6, suggesting diffuse fibrosis of the kidneys. The pathological examination led to a diagnosis of mesangial proliferative glomerulonephritis (moderate fibrosis of glomerulus and renal interstitium). HE and PAS staining (e, f) supported this diagnosis. The immunochemical examination (g, h) found FAP in the renal interstitium. Almost no FAP was found in the glomerulus, which was consistent with the PET/CT results.

Figure 5

A bar graph comparing the SUVmax (A), TBR (B), Scr (C), and GFR (D) of patients with different grades of renal fibrosis. The four sets of data revealed an obvious trend. Statistical significance of $p < 0.05$ was determined by one-way ANOVA (A, B, and C) and Kruskal-Wallis test (D) (degree of renal fibrosis=DORF).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

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