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SHORT COMMUNICATION

[^{18}F]FDG PET/CT imaging disproves renal allograft acute rejection in kidney transplant recipients with acute kidney dysfunction: a validation cohort

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Abstract

Purpose [^{18}F]FDG PET/CT may predict the absence of acute allograft rejection (AR) in kidney transplant recipients (KTRs) with acute kidney injury (AKI). Still, the proposed threshold of 1.6 of the mean of mean standardized uptake values (mSUVmean) in the renal parenchyma needs validation.

Methods We prospectively performed 86 [^{18}F]FDG PET/CT in 79 adult KTRs who underwent *per-cause* transplant biopsy for suspected AR. Biopsy-proven polyoma BK nephropathies (n = 7) were excluded. PET/CT was performed 192 ± 18 min after administration of 254.4 ± 30.4 MBq of [^{18}F]FDG. The SUV_{mean} was measured in both upper and lower poles of the renal allograft. One-way analysis of variance (ANOVA) and Tukey's studentized range test were sequentially performed. The receiver operating characteristic (ROC) curve was drawn to discriminate "AR" from non-pathological ("normal" + "borderline") conditions.

Results The median age of the cohort was 55 [43; 63] years, with M/F gender ratio of 47/39. The mean eGFR was 31.9 ± 14.6 ml/min/1.73m^2. Biopsies were categorized in 4 groups: "normal" (n = 54), "borderline" (n = 9), "AR" (n = 14), or "others" (n = 2). The median [min; max] $mSUV_{mean}$ reached 1.72 [1.02; 2.07], 1.97 [1.55; 2.11], 2.13 [1.65, 3.12], and 1.84 [1.57; 2.12] in "normal," "borderline," "AR," and "others" groups, respectively. ANOVA demonstrated a significant difference of $mSUV_{mean}$ among groups ($F = 13.25$, $p < 0.0001$). The ROC area under the curve was 0.86. Test sensitivity and specificity corresponding to the threshold value of 1.6 were 100% and 30%, respectively.

Conclusion [^{18}F]FDG PET/CT may help noninvasively prevent inessential transplant biopsies in KTR with AKI.

Keywords [^{18}F]FDG PET/CT · Kidney transplant · Acute rejection · Diagnosis · Banff

Introduction

The prompt diagnosis of acute kidney allograft rejection (AR) is crucial in the management of kidney transplant recipients (KTRs) presenting with acute kidney injury

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(AKI). It currently relies on the histological analysis of a renal sample obtained by needle biopsy, following Banff classification [1]. In clinical routine, most *per-cause* transplant biopsies show a normal histology [2]. Therefore, various non-invasive diagnostic approaches are under investigation to reduce the systematic usage of allograft biopsies [3–5]. More specifically, rodent models of allogeneic kidney transplantation (KTx) demonstrated that [^{18}F]FDG PET/CT early and specifically detect AR [6]. In humans, we have similarly underscored the putative usefulness of [^{18}F]FDG PET/CT in the diagnosis of AR in a pilot study of 32 KTRs with AKI [7]. Our "rule-out" approach was based on the mean of mean standardized uptake values ($mSUV_{mean}$) in 4 independent volumes of interest (VOI) of the renal cortex, with a diagnostic threshold set at 1.6 to target a negative predictive value of 100%. In the present validation cohort, we prospectively assess this 1.6 threshold of renal $mSUV_{mean}$ in the diagnosis of AR in KTRs with AKI who underwent a transplant needle biopsy for suspected AR.

Patients and methods

Patient population and specimens

The study was approved by ULiège IRB (#B707201215598). After written informed consent, adult KTRs undergoing a transplant biopsy for suspected AR were prospectively enrolled between March 2015 and December 2019.

Histopathology

Biopsies were assessed by two pathologists according to Banff criteria [1]. Histological lesions were scored as continuous variables (from 0 to 3) based on leukocyte infiltration in each component: glomeruli (g); peritubular capillaries (ptc); arteries (v); tubules (t); and interstitium (i). Biopsies diagnosed as "normal" were defined as a Banff [i + t] score < 2 and no features of a disease. Biopsies diagnosed as "borderline" were defined as a Banff [i + t] score ≥ 2 (but < i2-t2 and v = 0) and no feature of a specific disease. Biopsies diagnosed as "AR" were defined as a Banff [i + t] score ≥ i2 and ≥ t2 and/or v > 0. Biopsies diagnosed as "others" were defined as showing features of AR-unrelated diseases. All biopsies were stained for polyoma BK virus.

[^{18}F]FDG PET/CT imaging

The present validation cohort followed exactly the same protocol as described in the proof-of-concept study [7]. The PET/CT procedure was performed using cross-calibrated Philips GEMINI TF Big Bore or TF 16 PET/CT systems (Philips Medical Systems, Cleveland, OH, USA) at 191 [min. 179; max. 254] min following intravenous injection of a mean dose of 254.4 ± 30.4 MBq of [^{18}F]FDG (to purge as much as possible the radioactive signal from the urinary compartment). No contrast agent or diuretics were infused. A low-dose helical CT (5-mm slice thickness, 120-kV tube voltage, and 40-mAs tube current–time product) centered to the renal transplant was performed, followed by a PET emission scanning with 2 bed positions each lasting 4 min. Images were reconstructed using iterative list mode time-of-flight algorithms, and corrections for attenuation, dead-time, random, and scatter events were applied. The PET/CT procedure was performed within a 48-h period of the ultrasound-guided renal transplant biopsy. All [^{18}F]FDG -PET/CT were acquired in fasting conditions before any modification of immunosuppressive regimens. The mean glycemia at the time of tracer injection was 6.2 ± 1.6 mmol/L. Four VOI of 1 ml were manually drawn in the cortical region of both upper (n = 2) and lower (n = 2) poles of the renal transplant at distance from the pelvicalyceal zone, as described previously [8]. The SUV_{mean} was measured in each VOI, with no threshold activity, and the mean of these 4 SUV_{mean} was calculated ($mSUV_{mean}$).

Statistics

Data were expressed as mean ± standard deviation (SD) or as median [minimum; maximum]. One-way analysis of variance (ANOVA) followed by post hoc Tukey's studentized range test was performed to statistically compare $mSUV_{mean}$ values among groups taking into account the necessary correction for multiple testing. The receiver operating characteristic (ROC) curve was drawn to discriminate "AR" from non-pathological ("normal" + "borderline") conditions. The correlation between $mSUV_{mean}$ and acute composite (g + i + t + v + ptc) Banff score was calculated. All analyses were done with SAS 9.4.

Results

We performed 86 [^{18}F]FDG PET/CT in 79 KTR with AKI. Each suspicion of AR leading to kidney biopsy and [^{18}F]FDG PET/CT imaging was clinically and statistically independent. The characteristics of the cohort are summarized in Table 1. The median age was 55 [43; 63] years, with M/F gender ratio of 47/39. The mean eGFR was 31.9 ± 14.6 ml/min/1.73m^2. Biopsies were described as "normal" (n = 54), "borderline" (n = 9), "AR" (n = 14), or "others" (n = 2). Biopsy-proven polyoma BK nephropathies (n = 7) were excluded. AR was antibody-mediated in 2 cases, whereas T-cell-mediated AR was found in 13 cases, respectively. The histological finding in the "other"

Table 1 Clinical and biological characteristics of the cohort

	Cohort (n = 86 events)
Recipient	
Age (years)	55 [43; 63]
Gender (male/female; n)	47/39
BMI (kg/m^2)	27 [22; 30]
Donor	
Donor type (n), DBD/DCD/LD	63/17/6
Age (years)	43 ± 13
Gender (male/female; n)	40/46
Transplantation	
Rank 1st/ 2nd, or 3rd (n)	79/7
CIT (min)	644 ± 287
HLA mismatches, A + B + DR/6 (n)	3 [2; 4]
Early graft function, immediate/slow/DGF	51/26/9
Status at time of biopsy	
Maintenance immunosuppression (n) CNI, CsA/FK/none	8/75/3
Anti-metabolites (n) MMF/MPA/Aza/none	66/12/1/7
mTOR inhibitors: yes/no (n)	4/82
Steroids: yes/stop (n)	70/16
Duration KTx at biopsy (days)	279 [28; 1923]
Donor-specific antibodies: yes/no (n)	14/72

Data are expressed as mean ± standard deviation; median [interquartile range]

AZA, azathioprine; *BMI*, body mass index; *CIT*, cold ischemia time; *CNI*, calcineurin inhibitors; *CsA*, cyclosporin A; *DBD*, donor after brain death; *DCD*, donor after circulatory death; *DGF*, delayed graft function; *FK*, tacrolimus; *KTx*, kidney transplantation; *HLA*, human leukocyte antigen; *LD*, living donor; *MMF*, mycophenolate mofetyl; *MPA*, mycophenolic acid; *mTOR*, mechanistic target of rapamycin

causes of graft failure was focal segmental glomerulosclerosis with no evidence of AR (n = 2). The median [min; max] $mSUV_{mean}$ reached 1.72 [1.02; 2.07], 1.97 [1.55; 2.11], 2.13 [1.65; 3.12], and 1.84 [1.57; 2.12] in "normal," "borderline," "AR," and "others" groups, respectively (Fig. 1). ANOVA demonstrated a significant difference of $mSUV_{mean}$ among groups ($F = 13.25$, $p < 0.0001$) (Fig. 2A). The $mSUV_{mean}$ of biopsy-proven AR was significantly higher than "normal" cases ($p < 0.05$). There was no significant difference between "normal" vs. "borderline" or between "AR" vs. "borderline" groups. A positive correlation between $mSUV_{mean}$ and the acute Banff score was found, with adjusted r^2 of 0.41 ($p < 0.0001$) (Fig. 2B). The area under the ROC curve reached 0.86. Test sensitivity and specificity corresponding to the threshold value of 1.6 were 100% and 30%, respectively. Of methodological note, the Youden index reached 2.073, with a sensitivity of 57.1% and a specificity of 96.8%.

Discussion

In the present prospective validation cohort of 86 [^{18}F]FDG PET/CT performed in 79 KTRs presenting with AKI, the previously proposed $mSUV_{mean}$ threshold of 1.6 significantly discriminated non-rejection, with a sensitivity of 100% [7]. The poor specificity of [^{18}F]FDG PET/CT in detecting AR is most probably due to the radiotracer which accumulates in other inflammatory conditions. Still, the renal allografts with biopsy-proven AR were characterized by a significantly higher uptake of [^{18}F]FDG compared to "normal" biopsies, with a Youden index of 2.073 corresponding to a specificity of 96.8%. From a clinical point of view, a high negative predictive value appears more appropriate in the management of KTR with AKI in order to certify that no diagnosis of AR is missed or delayed. The pathophysiological hypothesis of such a preferential accumulation of [^{18}F]FDG in case of AR relies on the increased metabolic activity of infiltrating inflammatory cells, as suggested by the correlation between renal $mSUV_{mean}$ and leucocyte infiltration quantified by the acute Banff score [6]. The clinical significance and treatment of borderline changes remain highly debated, which prompts the ongoing development and validation of various biofluid-based biomarkers of clinically relevant AR [1, 5]. Note that the ROC curve comparing "normal" biopsies versus "biopsy-proven AR" after excluding the borderline cases was characterized by an AUC of 0.85, with a cut-off of 1.6 corresponding to 100% sensitivity and 30% specificity. All cases with biopsy-proven polyoma BK nephropathy were excluded from our analysis since the diagnostic procedure has been standardized via polymerase chain reaction (PCR)-based screening for BK virus replication in urine and/or blood specimens [9]. *Stricto sensu*, a needle biopsy of the renal allograft should only be performed after negative PCR results. The median $mSUV_{mean}$ of the allografts with biopsy-proven polyoma BK nephropathy was 2.20 [1.96; 2.47].

The limitations of our proposed non-invasive diagnostic approach based on [^{18}F]FDG PET/CT in unstable KTR with AKI include (i) the somewhat restricted availability of PET/CT machine, (ii) the minor exposure to radiations originating from both PET and CT procedures, and (iii) the 3-h delay between [^{18}F]FDG injection and image acquisition. Still, the repeatability and reproducibility of the quantification of kidney allograft [^{18}F]FDG uptake have been reported as consistent [8]. The use of multiple independent VOI distributed right beneath the renal capsule in both the upper and lower renal cortices aimed at (i) limiting the noise of the urinary [^{18}F]FDG and (ii) averting sampling error, which also represents one of the main limitations of transplant biopsy [1]. Of technical note, no

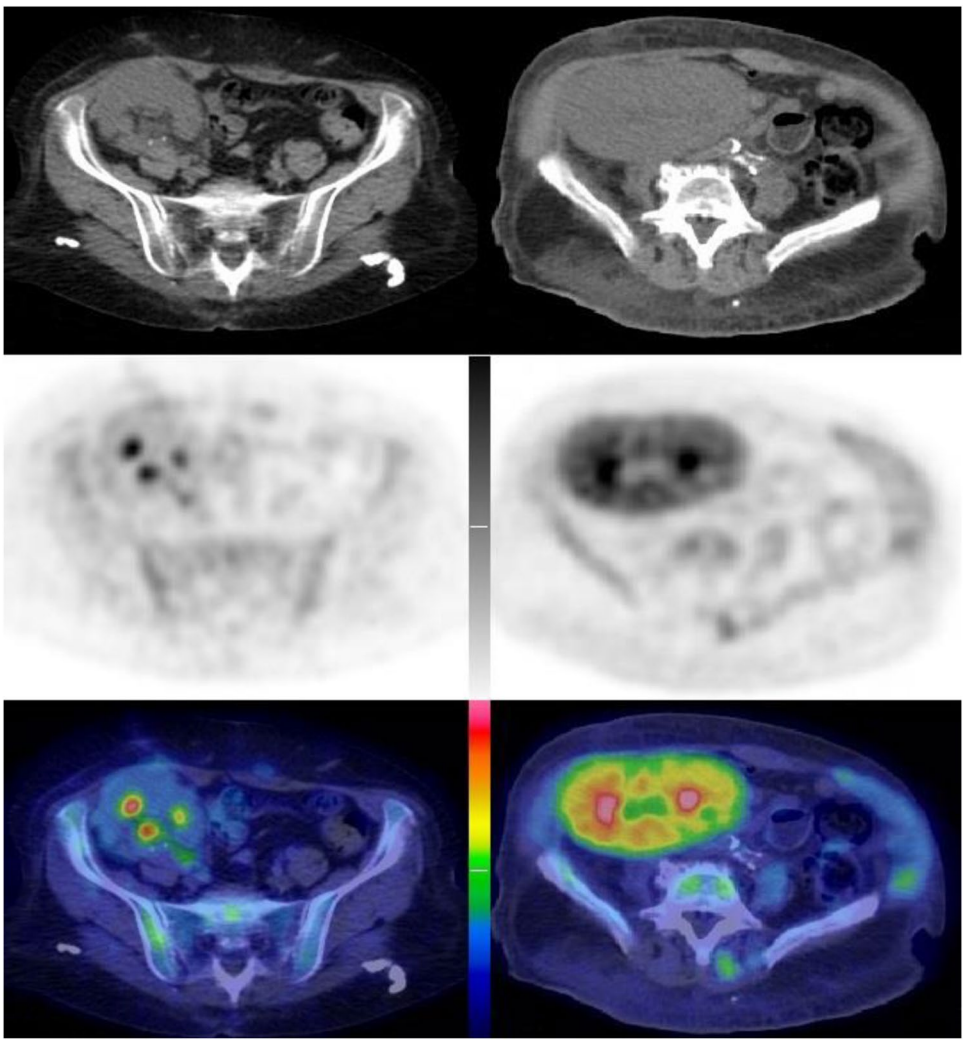

Fig. 1 Representative [^{18}F]FDG PET/CT imaging in kidney transplant recipients with biopsy-proven normal histology *versus* acute rejection. Positron-emission tomography (PET, top panels), computed tomography (CT, middle panels), and combined PET/CT images taken after administration of [^{18}F]FDG are shown for kidney transplant recipients with biopsies showing normal histology (left column; $mSUV_{mean}$ of 1.5; acute Banff score of 0) or T-cell-mediated acute rejection (right column; $mSUV_{mean}$ of 3.1; acute Banff score of 8). The arbitrary scale of standard uptake value (SUV, from 0 to 5) is illustrated

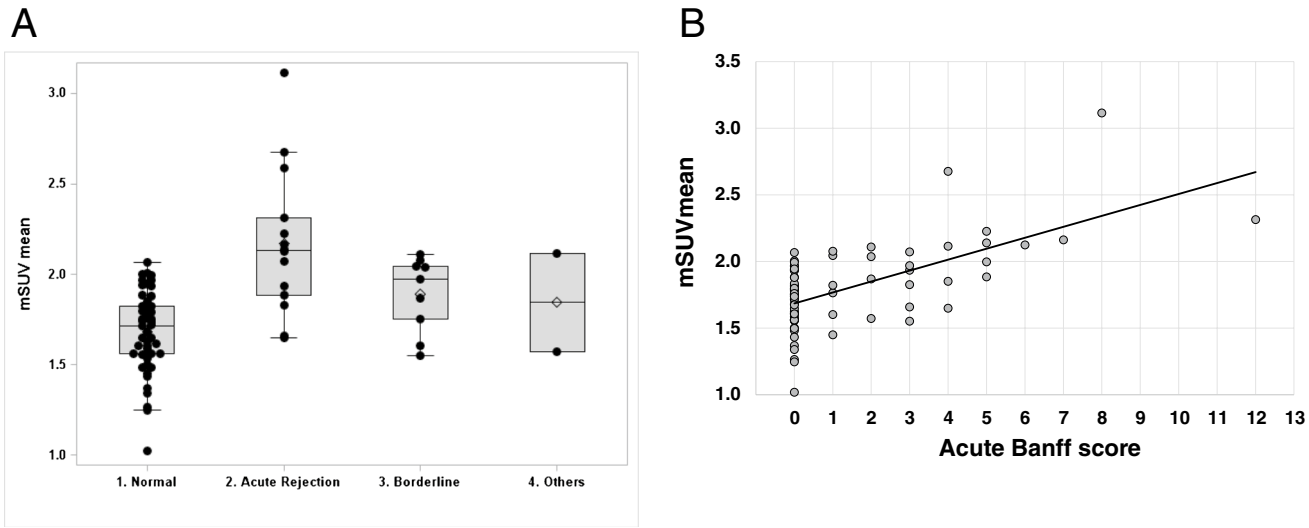

Fig. 2 Summary of the statistical results of ^{18}F-FDG PET/CT analysis. **A** Boxplot of the mean values of the renal allograft mean SUV_{mean} according to the histopathological categories: normal (n = 54); borderline (n = 9); acute rejection (AR) (n = 14); and others (n = 2). *ANOVA: F-score* = 13.25, *p-value* < 0.0001. **B** Positive correlation between the mean SUV_{mean} and the acute Banff score ($R^2 = 0.41$, *p-value* < 0.0001)

difference was statistically detected between the SUV_{mean} of the 4 VOI in the present 86-scan cohort. Assessing the global [^{18}F]FDG accumulation in the renal allograft by means of image segmentation software (currently under development and validation) would further help to minimize the sampling error.

On the basis of this validation cohort, we postulate that [^{18}F]FDG PET/CT as first-line examination may help save selected patients with AKI from undergoing kidney transplant biopsy. Such an invasive procedure would have been avoided in 19 cases of our series, which were characterized by an $mSUV_{mean}$ strictly inferior to the 1.6 threshold and a normal histology. Further large prospective multicentric studies are needed to test whether the $mSUV_{mean}$ threshold of [^{18}F]FDG PET/CT imaging, in combination with blood and urinary biomarkers [3–5], helps to pragmatically dictate the need for transplant biopsy in KTR presenting with AKI and suspected AR. Other tracers for inflammation may also be envisioned in this frequent clinical scenario, such as [^{11}C] methionine or [^{68} Ga]pentixafor. Standard nuclear medicine imaging methods, including MAG3 renal scintigraphy, may also provide essential information about perfusion and function of the kidney in clinical conditions of suspected AR or acute tubular necrosis [10].

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Author contribution LP, LW, RH, and FJ designed the study; RH and FJ secured the funding of the study; HP performed the statistical analyses; LW, AB, and CB recruited the patients and filled the medical files; AB performed the kidney biopsies; CB and SG scored the biopsies; LP and RH scored the [^{18}F]FDG PET/CT images; LP and FJ wrote the manuscript; all authors approved the final version of the manuscript.

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Data availability The data will be made available on request.

Code availability N/A.

Declarations

Ethics approval The study was approved by the institutional review board of the ULiège Academic Hospital (#B707201215598).

Consent to participate After written informed consent, adult KTRs undergoing a transplant biopsy for suspected AR were prospectively enrolled between March 2015 and December 2019.

Conflicts of interest The authors declare no competing interests.

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