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A Pilot Trial to Examine the Changes in Carotid Arterial Inflammation in Renal Transplant Recipients as Assessed by ^{18}F-Fluorodeoxyglucose (^{18}F-FDG) Positron Emission Tomography Computed Tomography (PET/CT)

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: Inflammatory activity of the artery can be assessed by measuring ^{18}F-fluorodeoxyglucose (^{18}F-FDG) uptake with positron emission tomography computed tomography (PET/CT). Improvement in vascular function after renal transplantation has been reported, but no studies have used ^{18}F-FDG PET/CT to examine the changes in vascular inflammation. This study investigated the changes in the inflammatory activity in the carotid artery after renal transplantation in patients with chronic kidney disease (CKD).

Material/Methods: ^{18}F-FDG PET/CT was performed before and at 4 months after transplantation. We quantified ^{18}F-FDG uptake as the target-to-background ratio (TBR) in the carotid artery in 10 CKD patients. TBR was evaluated in the whole carotid artery (WH) and most-diseased segment (MDS), and the mean and maximum values were analyzed. The concentrations of inflammatory cytokines, including tumor necrosis factor-alpha, interleukin-6, plasminogen activator inhibitor-1, and endothelin-1, were measured.

Results: Eight patients showed a decrease in mean or maximum TBR. The average mean or maximum TBRs in the WH and MDS of the right and left arteries were all reduced after transplantation. The average mean TBR for the right WH decreased significantly (% reduction [95% CI]) by –5.74% [–15.37, –0.02] (p=0.047). TBRs did not correlate significantly with cytokine concentrations. The changes in cytokine concentrations after transplantation varied.

Conclusions: ^{18}F-FDG uptake by the WH and MDS tended to reduce after renal transplantation. Therefore, renal transplantation may confer an anti-inflammatory effect on carotid atherosclerosis in patients with CKD; however, this effect is not large enough to be demonstrated in this study with small sample size.

MeSH Keywords: **Atherosclerosis • Carotid Artery Diseases • Fluorodeoxyglucose F18 • Kidney Transplantation • Positron-Emission Tomography • Renal Insufficiency, Chronic**

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Background

Patients with chronic kidney disease (CKD) have an extremely high risk of developing cardiovascular disease (CVD), which is the leading cause of death in this population [1,2]. Traditional risk factors for CVD in CKD patients are hypertension, diabetes, dyslipidemia, and smoking [3]. However, traditional risk factors underestimate the CVD risk in CKD patients [4]. Renal transplantation has a survival advantage over dialysis and reduces the CVD risk even with the persistence of traditional risk factors [5–7]. These findings imply a role of CKD-related, nontraditional risk factors in the development of CVD. Inflammation is one of the main contributing factors to the increased CVD risk in CKD patients. C-reactive protein (CRP), a marker of inflammation, predicts progression of atherosclerosis [8] and increased CVD risk in CKD patients [9]. CRP levels have been shown to decrease [10,11], and carotid intima-media thickness (IMT) [11], endothelial function [12–14], and aortic stiffness [15] to improve after renal transplantation. These changes may be associated with the reduced CVD risk in CKD patients.

^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography computed tomography (PET/CT) is an imaging technique frequently used for cancer surveillance. Atherosclerotic plaque inflammation can be imaged with ^{18}F-FDG PET/CT by assessing the increased ^{18}F-FDG uptake by the arterial wall [16,17]. The arterial ^{18}F-FDG uptake is an independent predictor for future CVD beyond that predicted by the Framingham risk score [18]. Increased arterial inflammation measured by ^{18}F-FDG uptake using ^{18}F-FDG PET/CT was reported recently in CKD patients without overt atherosclerotic disease [19]. However, it is unknown whether the inflammatory activity of the carotid artery decreases after renal transplantation. In this study, we evaluated the changes in arterial inflammatory activity after renal transplantation by measuring ^{18}F-FDG uptake by carotid arteries using ^{18}F-FDG PET/CT.

Material and Methods

Patients and study design

This study was a prospective, single-center trial to evaluate the changes in inflammatory activity of the carotid artery after renal transplantation. Ten patients with stage 5 CKD who were planning to receive a living-donor renal transplant were enrolled between January 2014 and June 2016. The exclusion criteria were prior stroke or acute myocardial infarction, previous percutaneous coronary intervention or coronary artery bypass graft surgery, use of statin treatment within the previous 4 months, age less than 18 years, or pregnancy. After enrollment, patients underwent a baseline ^{18}F-FDG PET/CT scan before renal transplantation and any immunosuppressive or desensitization therapy and were followed by a second ^{18}F-FDG PET/CT scan at 4 months after renal transplantation. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the institutional review board of Incheon St. Mary's Hospital (OC13OISI0113). All patients provided written informed consent. The clinical and research activities being reported are consistent with the Principles of the Declaration of Istanbul as outlined in the "Declaration of Istanbul on Organ Trafficking and Transplant Tourism".

^{18}F-FDG PET/CT and image analysis

^{18}F-FDG PET/CT scans were performed as previously published (Discovery Ste, GE Healthcare) [18,20]. ^{18}F-FDG PET/CT images were analyzed as previously described [21]. Arterial ^{18}F-FDG uptake was measured in the right and left carotid arteries every 3 mm starting 2 cm below the carotid artery bifurcation and continuing superiorly to 2 cm into the internal carotid artery. The intensity of ^{18}F-FDG uptake was quantified by measuring the maximum and mean standardized uptake value (SUV) corrected for body weight. The SUV score of the artery was corrected for background venous activity by dividing the average blood SUV estimated from the internal jugular veins and was defined as the target-to-background ratio (TBR). TBR was evaluated in the whole carotid artery (WH) and the most-diseased segment (MDS). The MDS, in turn, was defined as the 1.5 cm arterial segment, centered on the slice of artery, demonstrating the highest ^{18}F-FDG uptake at baseline. TBR was assessed using 2 different approaches. The first approach was to define the average maximum TBR activity. WH-TBR$_{max}$ was calculated as the average maximum TBR of the WH segments. MDS-TBR$_{max}$ was calculated as the average maximum TBR derived from 3 contiguous axial segments of the MDS. The second approach was to define the average mean TBR activity. WH-TBR$_{mean}$ was calculated as the average mean TBRs for the WH segments. MDS-TBR$_{mean}$ was calculated as the average mean TBRs of the MDS. Among the 2 carotid arteries, the artery with the highest ^{18}F-FDG uptake at baseline was identified as the index vessel, as previously described [21,22]. The index vessel TBR was calculated using 2 different approaches; calculating WH-TBR$_{max}$ and MDS-TBR$_{max}$ of the index vessel. Two nuclear medicine physicians who were uninformed of the study protocol made the ^{18}F-FDG uptake measurements, and then the 2 measurements were averaged.

Outcome definitions

The primary objective of this study was to evaluate whether renal transplantation reduced the TBRs of the WH and MDS from baseline. The absolute and percent changes in the average maximum TBRs within the WH (WH-TBR$_{max}$) and the MDS (MDS-TBR$_{max}$) were assessed. The absolute and percent changes in the average mean TBRs within the WH (WH-TBR$_{mean}$) and

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the MDS (MDS-TBR$_{mean}$) were also assessed. The changes in TBRs were analyzed separately in the right and left carotid arteries, and the changes in the WH-TBR$_{max}$ and MDS-TBR$_{max}$ of the index vessel were analyzed.

Laboratory examinations

Venous blood samples were obtained from all patients after a 12-hour overnight fast at the same time points used for the ^{18}F-FDG PET/CT scans. Enzyme immunoassay assays were used to measure the concentrations of tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), plasminogen activator inhibitor-1 (PAI-1), and endothelin-1 (all from R&D Systems, Minneapolis, MN, USA). Serum CRP concentration was measured using a high-sensitivity immunoturbidimetric method. Renal function was calculated using the Modification of Diet in Renal Disease formula for estimated glomerular filtration rate (eGFR) [23]. Changes in the concentrations of TNF-α, IL-6, PAI-1, endothelin-1, eGFR, CRP, total cholesterol (TC), triglyceride, low-density lipoprotein-cholesterol (LDL-C), and high-density lipoprotein-cholesterol (HDL-C) were also analyzed.

Statistical analyses

The data are expressed as median and interquartile range (IQR). The Wilcoxon signed-rank test was used to assess differences in the TBRs and other parameters before and after renal transplantation. Associations between the TBR of the MDS-TBR$_{max}$ of the index vessel and other variables were tested using Spearman correlation analysis. Statistical analyses were performed using the Statistical Analysis Software package (SAS version 9.1, SAS Institute, Cary, North Carolina, USA). A *p* value of less than 0.05 was considered statistically significant.

Results

Baseline characteristics

Table 1 shows the baseline characteristics of the 10 patients. The median age (IQR) was 48 years (36.75, 58.25). Four patients (40%) were men, and 5 patients (50%) had diabetes mellitus. None of the patients had previous CVD, and 6 patients (60%) had visible plaque on carotid ultrasound. One patient (10%) had a panel-reactive antibody level of more than 50%, none had donor-specific antibody, and 4 patients (40%) received an ABO-incompatible renal transplantation. For desensitization therapy, 1 patient (10%) received rituximab only, and 4 patients (40%) received rituximab, plasmapheresis, and intravenous immunoglobulin. Corticosteroids were tittered to a dose of 5 or 10 mg/day by the time of the second ^{18}F-FDG PET/CT scan in all patients.

Table 1. Baseline characteristics.

		N=10
Age, years, median (IQR)	48.0	(36.75, 58.25)
Recipient male, n (%)	4	(40)
Diabetes mellitus, n (%)	5	(50)
Cause of ESRD, n (%)		
Diabetes	5	(50)
Hypertension	1	(10)
Chronic GN	2	(20)
Others	2	(20)
Previous CV disease, n (%)	0	(0)
History of smoking, n (%)	3	(30)
BMI, kg/m^2, median (IQR)	22.37	(20.13, 27.93)
Dialysis vintage, months, median (IQR)	3.36	(1.45, 24.53)
eGFR, ml/min/1.73 m^2, median (IQR)	5.38	(4.29, 6.75)
Donor male, n (%)	6	(60)
Donor age, years, median (IQR)	41.50	(35.0, 52.75)
Systolic BP (mmHg), median (IQR)	140.0	(120.0, 150.0)
Diastolic BP (mmHg) median (IQR)	80.0	(77.50, 92.50)
LV ejection fraction (%), median (IQR)	62.5	(58.5, 68.3)
Rt carotid IMT (mm), median (IQR)	0.60	(0.55, 0.90)
Lt carotid IMT (mm), median (IQR)	0.65	(0.58, 1.08)
Carotid plaque on US, n (%)	6	(60)
TC, mg/dL	167.0	(146.0, 239.0)
Triglyceride, mg/dL	132.50	(95.25, 220.50)
HDL-cholesterol, mg/dL	36.50	(27.0, 53.50)
LDL-cholesterol, mg/dL	100.0	(88.50, 167.0)
HLA mismatch No, median (IQR)	3.0	(1.75, 4.0)
Panel reactive antibody >50%, n (%)	1	(10)
Presence of DSA, n (%)	0	(0)
ABO incompatible, n (%)	4	(40)
Induction therapy		
Basiliximab	10	(100)
Anti-thymocyte globulin	0	(0)
Maintenance immunosuppression		
Tacrolimus (%)	10	(100)
Mycophenolate mofetil (%)	10	(100)
Desensitization therapy		
Rituximab only (%)	1	(10)
Rituximab/Plasmapheresis/IVIG (%)	4	(40)
None	5	(50)

IQR – interquartile range; ESRD – end-stage renal disease; BP – blood pressure; CVD – cardiovascular disease; eGFR – estimated glomerular filtration rate; BP – blood pressure; LV – left ventricular; IMT – intima-media thickness; TC – total cholesterol; HDL-C – high-density lipoprotein-cholesterol; LDL-C – low-density lipoprotein-cholesterol; HLA – human leukocyte antigen; IVIG – intravenous immunoglobulin.

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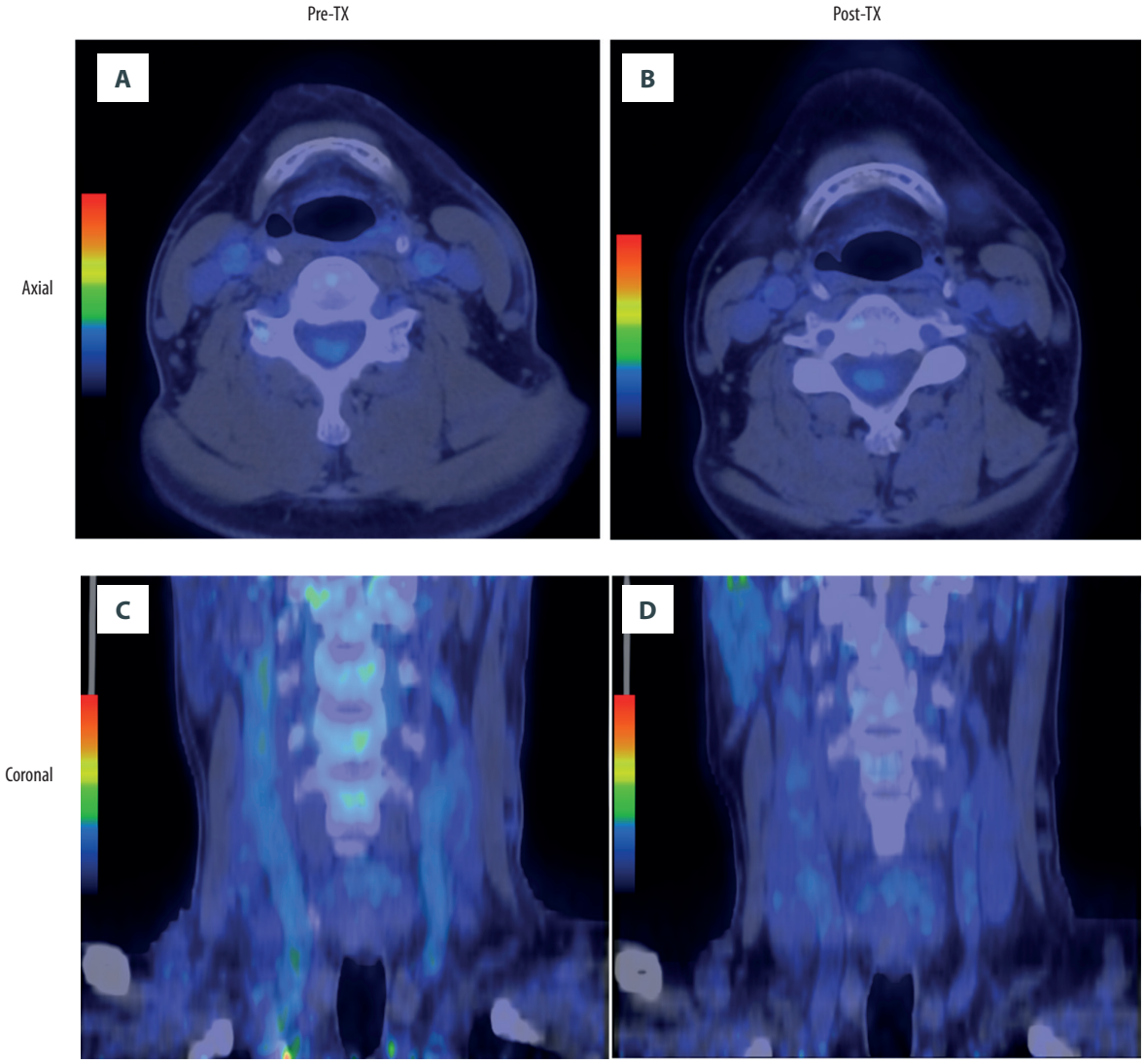

Figure 1. Representative images of ^{18}F-FDG PET/CT of carotid artery before and after renal transplantation. The upper row is axial images (**A, B**), and the lower row is coronal images (**C, D**). Note the reduction in ^{18}F-FDG uptake in both carotid arteries after transplantation (**B, D**) compared to baseline (**A, C**). Pre-Tx – before renal transplantation; Post-Tx – after renal transplantation.

Changes in carotid arterial inflammatory activity after renal transplantation

The ^{18}F-FDG uptake by both carotid arteries was compared between the baseline and after transplantation using the axial and coronal images of ^{18}F-FDG PET/CT scans (Figure 1). The changes in TBRs in the WH and MDS of the right and left carotid arteries are shown in Figures 2 and 3, respectively. Eight of the 10 patients (80%) showed a reduction in right WH-TBR$_{max}$ and WH-TBR$_{mean}$, and left MDS-TBR$_{mean}$, WH-TBR$_{max}$, and WH-TBR$_{mean}$. Seven patients (70%) showed a reduction in right MDS-TBR$_{max}$ and MDS-TBR$_{mea}$n, and left MDS-TBR$_{max}$. Figure 4 shows the changes in WH-TBR$_{max}$ and MDS-TBR$_{max}$ in the index vessel. Eight of the 10 patients (80%) showed a reduction in WH-TBR$_{max}$ and MDS-TBR$_{max}$ in the index vessel.

Table 2 shows the absolute and percent changes in TBRs. These tendencies were observed for reductions in right WH-TBR$_{max}$, MDS-TBR$_{max}$, and MDS-TBR$_{mean}$ (% reduction [95% CI]): –6.50% [–12.81, 1.54]; –4.06% [–13.42, 9.38]; and –4.47% [–13.64, 7.29], respectively. Tendencies were also observed for reductions in left WH-TBR$_{max}$, WH-TBR$_{mean}$, MDS-TBR$_{max}$, and MDS-TBR$_{mean}$ (% reduction [95% CI]) by –6.13% [–15.17, 8.32]; –8.37% [–17.62, 6.56]; –6.14% [–14.53, 7.01]; and –7.29% [–17.91,

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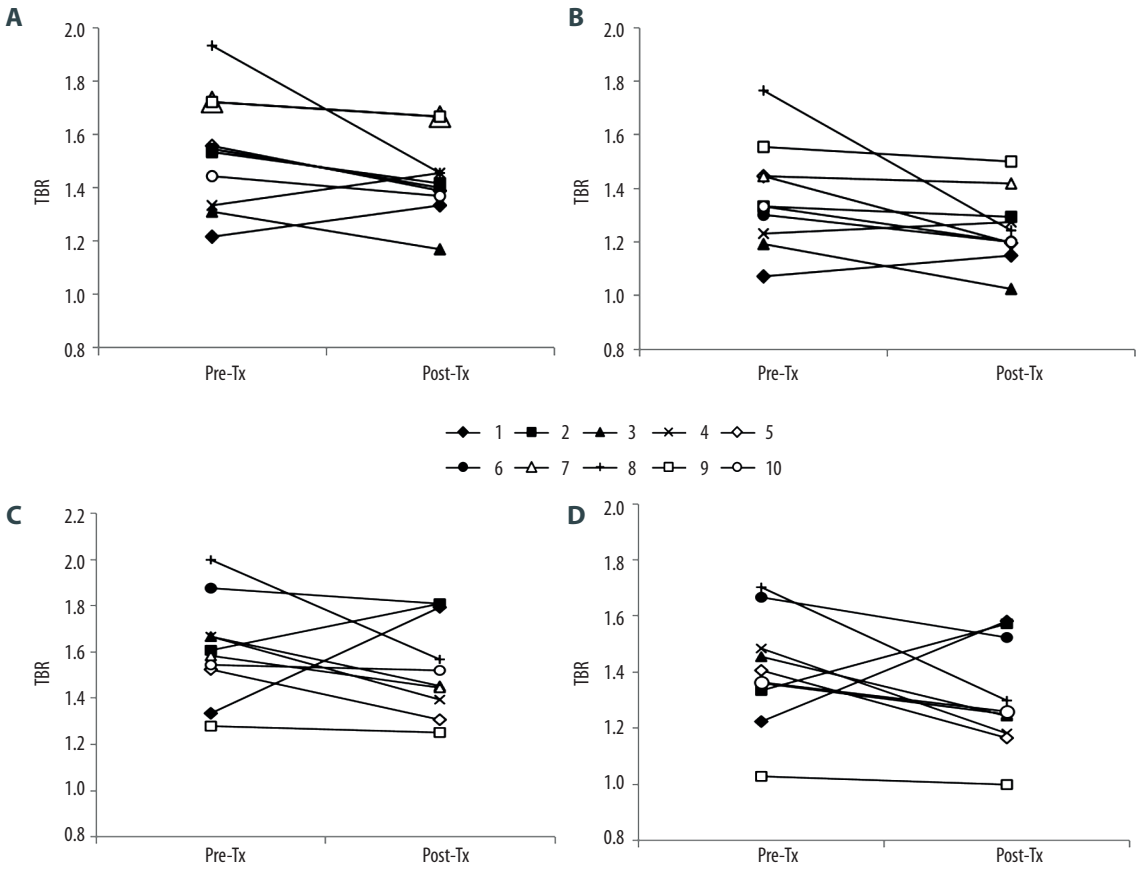

Figure 2. Changes in TBR values of right and left WH in individual participants after renal transplantation. (**A**) WH-TBR$_{max}$ of right carotid artery. (B)WH-TBR$_{mean}$ of right carotid artery. (**C**) WH-TBR$_{max}$ of left carotid artery. (**D**) WH-TBR$_{mean}$ of left carotid artery. Pre-Tx – before renal transplantation; Post-Tx – after renal transplantation; TBR – target-to-background ratio.

4.18], respectively. The right WH-TBR$_{mean}$ was significantly reduced from baseline (% reduction [95% CI] by –5.74% [–15.37, –0.02], p=0.047). In the index vessel, the WH-TBR$_{max}$ and MDS-TBR$_{max}$ tended to decrease from baseline (% reduction [95% CI]) by –3.36 [–14.11, 8.88] and –5.87 [–13.83, 6.80], respectively.

Change in eGFR and concentrations of CRP, lipids, and cytokines

Table 3 shows the changes in eGFR, laboratory results, and cytokine levels. The eGFR and total cholesterol and HDL-C concentrations increased significantly from baseline. The TNF-α and endothelin-1 concentrations did not change after renal transplantation, but the IL-6 and PAI-1 concentrations increased significantly after renal transplantation. The changes in cytokine concentrations were analyzed further according the administration of rituximab. TNF-α concentration did not change significantly in rituximab-treated patients but decreased significantly in rituximab-untreated patients. IL-6 concentration increased significantly in rituximab-treated patients but did not change significantly in rituximab-untreated patients. PAI-1 concentration increased significantly in both rituximab-treated and untreated patients. Endothelin-1 concentration did not change significantly in rituximab-treated or untreated patients.

Relationships between carotid arterial inflammatory activity and other variables

The relationships between the TBR of the index vessel and other variables were analyzed. In the index vessel, no significant correlations were observed between MDS-TBR$_{max}$ and the eGFR (rho=–0.32, p=0.16) or with the concentrations of TC (rho=–0.07, p=0.76), TG (rho=–0.18, p=0.45), LDL-C (rho=–0.05, p=0.85), HDL-C (rho=–0.11, p=0.64), CRP (rho=–0.03, p=0.92), TNF-α (rho=–0.07, p=0.78), PAI-1 (rho=–0.31, p=0.18), or endothelin-1 (rho=–0.15, p=0.52). A significant correlation was observed between MDS-TBR$_{max}$ and IL-6 concentration (rho=–0.46, p=0.044). The WH-TBR$_{max}$ of the index vessel did not correlate significantly with the eGFR (rho=–0.20, p=0.41) or with the concentrations of TC (rho=–0.02, p=0.95), TG (rho=–0.12, p=0.62), LDL-C

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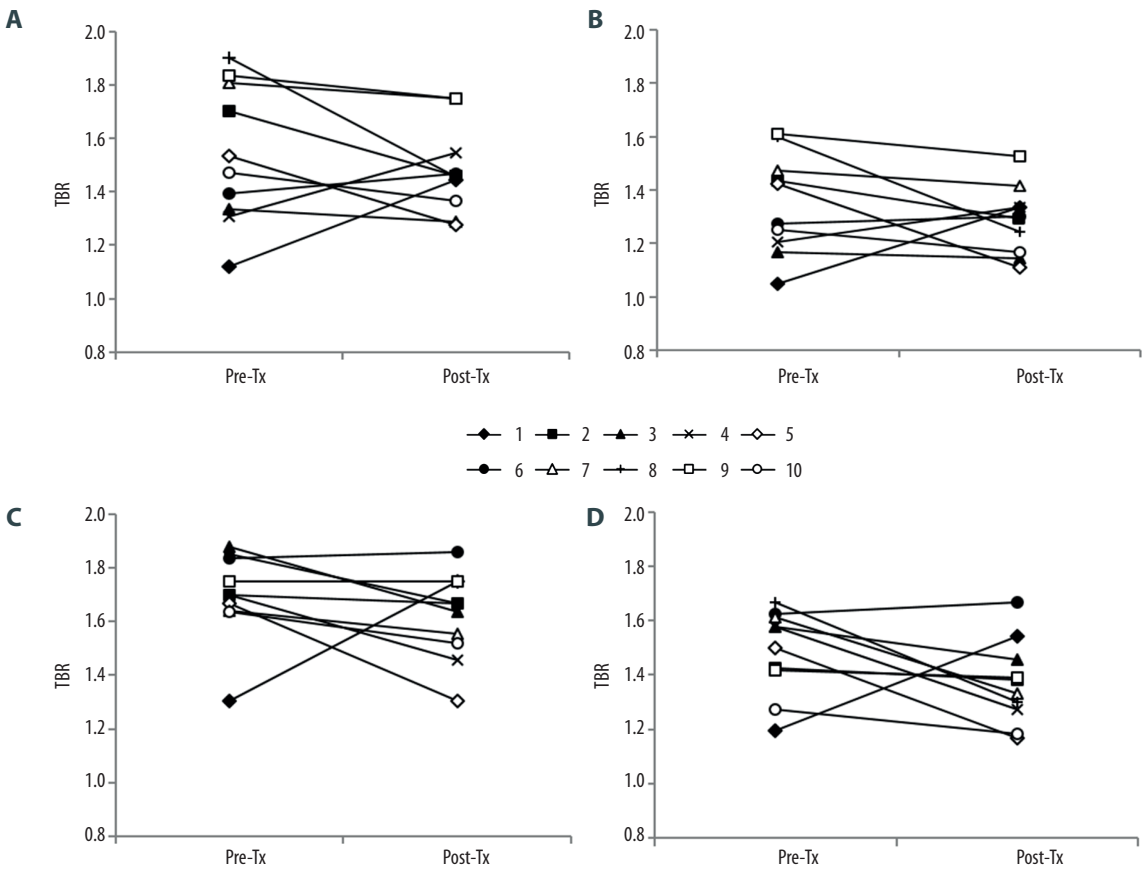

Figure 3. Changes in TBR values of right and left MDS in individual participants after renal transplantation. (**A**) MDS-TBR$_{max}$ of right carotid artery. (**B**) MDS-TBR$_{mean}$ of right carotid artery. (**C**) MDS-TBR$_{max}$ of left carotid artery (**D**) MDS-TBR$_{mean}$ of left carotid artery. Pre-Tx – before renal transplantation; Post-Tx – after renal transplantation; TBR – target-to-background ratio.

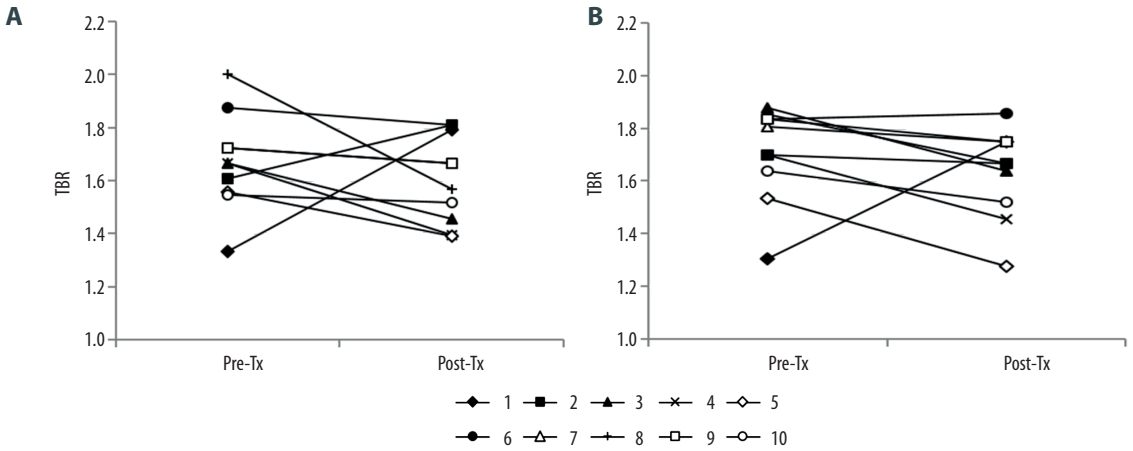

Figure 4. Changes in TBR values of the index vessel in individual participants after renal transplantation. (**A**) WH-TBR$_{max}$ of the index vessel. (**B**) MDS-TBR$_{max}$ of the index vessel. Pre-Tx – before renal transplantation; Post-Tx – after renal transplantation; TBR – target-to-background ratio.

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Table 2. Change in TBR in the WH and MDS.

	Baseline, median (IQR)		Post-transplantation, median (IQR)		% change from baseline, median (95% CI)		*P*
WH							
Right TBR_{max}	1.54	(1.33, 1.72)	1.41	(1.36, 1.51)	–6.50	(–12.81, 1.54)	0.09
Right TBR_{mean}	1.33	(1.22, 1.47)	1.22	(1.18, 1.32)	–5.74	(–15.37, –0.02)	0.047
Left TBR_{max}	1.59	(1.48, 1.72)	1.49	(1.37, 1.80)	–6.13	(–15.17, 8.32)	0.20
Left TBR_{mean}	1.38	(1.31, 1.53)	1.25	(1.18, 1.54)	–8.37	(–17.62, 6.56)	0.22
MDS							
Right TBR_{max}	1.50	(1.33, 1.81)	1.46	(1.35, 1.60)	–4.06	(–13.42, 9.38)	0.33
Right TBR_{mean}	1.35	(1.20, 1.50)	1.30	(1.16, 1.35)	–4.47	(–13.64, 7.29)	0.24
Left TBR_{max}	1.70	(1.64, 1.84)	1.65	(1.50, 1.75)	–6.14	(–14.53, 7.01)	0.14
Left TBR_{mean}	1.54	(1.38, 1.61)	1.36	(1.25, 1.48)	–7.29	(–17.91, 4.18)	0.09
Index vessel							
WH-TBR_{max}	1.67	(1.55, 1.76)	1.62	(1.44, 1.80)	–3.36	(–14.11, 8.88)	0.24
MDS-TBR_{max}	1.75	(1.61, 1.84)	1.67	(1.50, 1.75)	–5.87	(–13.83, 6.80)	0.09

IQR – interquartile range; CI – confidence interval; WH – whole carotid artery; TBR_{max} – maximum target-to-background ratio; TBR_{mean} – mean target-to-background ratio; MDS – most-diseased segment.

Table 3. Change in eGFR, CRP, lipids, and cytokine levels.

	Baseline, median (IQR)		Post-transplantation, median (IQR)		*P*
eGFR, ml/min/1.73 m^2	5.38	(4.29, 6.75)	71.97	(55.08, 78.04)	0.005
CRP, mg/L	0.42	(0.34, 0.50)	0.55	(0.37, 1.32)	0.24
TC, mg/dL	167.0	(146.0, 239.0)	237.0	(217.25, 293.0)	0.02
Triglyceride, mg/dL	132.50	(95.25, 220.50)	162.0	(129.0, 204.75)	0.72
HDL-cholesterol, mg/dL	36.50	(27.0, 53.50)	55.0	(41.50, 75.50)	0.047
LDL-cholesterol, mg/dL	100.0	(88.50, 167.0)	142.50	(133.75, 168.25)	0.074
TNF-α, pg/mL	14.95	(13.87, 18.25)	13.42	(11.62, 16.38)	0.45
Rituximab-untreated group (n=5)	15.13	(13.60, 18.19)	12.07	(11.16, 13.87)	0.04
Rituximab-treated group (n=5)	14.76	(13.62, 18.55)	15.41	(12.86, 25.00)	0.50
IL-6, pg/mL	3.50	(2.67, 6.04)	15.49	(4.12, 320.09)	0.03
Rituximab-untreated group (n=5)	3.60	(2.88, 6.18)	5.55	(3.50, 143.01)	0.50
Rituximab-treated group (n=5)	3.16	(2.63, 4.95)	23.33	(5.94, 655.10)	0.04
PAI-1, ng/mL	1.25	(0.94, 1.47)	3.57	(2.59, 4.56)	0.005
Rituximab-untreated group (n=5)	1.20	(0.91, 1.41)	4.13	(2.44, 4.65)	0.04
Rituximab-treated group (n=5)	1.29	(0.68, 1.72)	3.10	(2.43, 4.43)	0.04
Endothelin-1, pg/mL	297.25	(253.35, 395.23)	334.85	(280.88, 423.25)	0.51
Rituximab-untreated group (n=5)	302.20	(214.90, 377.30)	371.30	(257.85, 441.60)	0.23
Rituximab-treated group (n=5)	292.30	(271.35, 410.05)	311.40	(259.55, 411.10)	0.69

IQR – interquartile range; eGFR – estimated glomerular filtration rate; CRP – C-reactive protein; TC – total cholesterol; HDL-C – high-density lipoprotein-cholesterol; LDL-C – low-density lipoprotein-cholesterol; TNF-α – tumor necrosis factor-alpha; IL-6 – interleukin-6; PAI-I – plasminogen activator inhibitor-1.

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(rho=–0.16, p=0.50), HDL-C (rho=–0.04, p=0.86), CRP (rho=0.27, p=0.24), IL-6 (rho=–0.22, p=0.35), TNF-α (rho=0.15, p=0.53), PAI-1 (rho=–0.24, p=0.30), or endothelin-1 (rho=0.16, p=0.51).

Discussion

The results of the present study showed that the ^{18}F-FDG uptake by the carotid arteries of CKD patients decreased after renal transplantation. Seven or 8 of the 10 patients showed a reduction in ^{18}F-FDG uptake by the WH or MDS. The WH-TBR$_{mean}$ of the right carotid artery was significantly reduced from baseline. The MDS-TBR$_{max}$, MDS-TBR$_{mean}$, and WH-TBR$_{max}$ of both carotid arteries and the WH-TBR$_{mean}$ of the left carotid artery showed a tendency for a reduction from baseline. These findings suggest that renal transplantation may confer an anti-inflammatory effect on carotid atherosclerosis in CKD patients.

Only a few studies have used imaging techniques to examine the change in vascular disease after renal transplantation in CKD patients [24]. Carotid IMT is a surrogate marker for atherosclerosis [25] and is associated with inflammation in CKD patients [26,27]. One study found that carotid IMT improved after renal transplantation [11]. However, it was unclear whether the inflammatory activity in the carotid artery was reduced after renal transplantation. ^{18}F-FDG PET/CT is approved as an imaging technique for the assessment of atherosclerotic plaque inflammation [16,17]. Arterial ^{18}F-FDG uptake is associated with atherosclerosis progression [28] and independently predicts future CVD [18]. Studies have reported the use of ^{18}F-FDG PET/CT to monitor inflammation in the vessel wall during certain pharmacological and nonpharmacological interventions [21,22,29,30].

It has recently been shown that CKD patients without overt atherosclerotic disease have increased arterial ^{18}F-FDG uptake [19]. In this study, we included CKD patients without overt atherosclerotic disease and only those who had not received statin treatment within the previous 4 months because statins can attenuate atherosclerotic inflammation [21]. Previous studies using ^{18}F-FDG PET/CT have evaluated the changes in WH-TBR$_{max}$ and MDS-TBR$_{max}$ in the index vessel [21,22,29,30]. The MDS represents the site of the most severe inflammation in the vessel, whereas the WH is a mixture of more or less diseased segments; therefore, the treatment effects may be larger in the MDS than in the WH [21]. Although not statistically significant, the percent change was larger in the MDS-TBR$_{max}$ than in the WH-TBR$_{max}$ in the index vessel. We also calculated the TBR$_{max}$ and TBR$_{mean}$ of the WH and MDS in the right and left carotid arteries because our aim was to assess the various aspects of changes in carotid atherosclerosis. Although not all patients showed a reduction in carotid ^{18}F-FDG uptake, 70–80% of patients showed a reduction. A trend for a reduced ^{18}F-FDG uptake was observed, and the right WH-TBR$_{mean}$ was significantly reduced from baseline.

The literature shows that endothelial function improves within 1 month after transplantation [12,13]. However, we did not observe a marked reduction in the arterial inflammatory activity. The reason for this discrepancy is unclear but may be because our patients were receiving various immunosuppressive agents. It has been reported that rituximab improves endothelial function and reduces inflammation in patients with rheumatoid arthritis [31]. Mycophenolate mofetil was shown to decrease atherosclerotic lesion size in an animal study [32] and to attenuate plaque inflammation in patients with carotid artery stenosis [33]. By contrast, tacrolimus is associated with vascular inflammation and endothelial dysfunction in animal models [34,35] and in endothelial and vascular smooth muscle cells [36]. These drugs may interfere with each other's effects on the process of atherosclerosis. Additionally, the vascular response may be affected by several confounders such as diabetes mellitus or the use of antidiabetic or antihypertensive drugs.

We measured the concentrations of proinflammatory, prothrombotic, and vasoconstrictive cytokines to determine whether these cytokine changes correlate with the changes in arterial ^{18}F-FDG uptake. IL-6 and PAI-1 concentrations increased after renal transplantation, whereas TNF-α and endothelin-1 concentrations did not change significantly. Rituximab can increase the production of the proinflammatory cytokines TNF-α and IL-6 [37–39], and the cytokine levels changed differently according to the administration of rituximab. The decrease in TNF-α concentration in rituximab-untreated patients was noteworthy. PAI-1 is a prothrombotic cytokine, and its concentration increased in both rituximab-treated and untreated patients. Renal transplantation does not reverse coagulopathy in CKD patients [40]. Endothelin-1, a vasoconstrictive cytokine, also did not change significantly in either rituximab-treated or untreated patients. Our results differ from those of a previous report that showed a decrease in endothelin-1 concentration at 3 months after transplantation [15]. However, it has also been reported that endothelin-1 concentration does not correlate with the IMT in peripheral arteries in CKD patients [41]. These findings may suggest that changes in these cytokine concentrations do not correlate with the early changes in arterial ^{18}F-FDG uptake. Probably the time window for detection was too soon that cytokines levels are unlikely to stabilize four months after transplantation

Our study has several limitations. First, the number of patients was small and not all patients showed a consistent pattern of change in arterial ^{18}F-FDG uptake. Second, the follow-up ^{18}F-FDG PET/CT was taken at a relatively short interval after transplantation because previous studies reported that

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endothelial function improves within 1 month after transplantation [12,13], and because previous interventional studies using ^{18}F-FDG PET/CT to monitor arterial inflammation have taken follow-up ^{18}F-FDG PET/CT within 4 months from baseline [21,29]. Our results did not show the long-term effects of renal transplantation on carotid atherosclerotic inflammation. Third, an effect of immunosuppressive agents on carotid inflammation cannot be excluded.

Conclusions

Serial ^{18}F-FDG-PET/CT of the carotid arteries showed that the ^{18}F-FDG uptake by the WH and MDS was reduced in the early post-transplantation period. Renal transplantation may confer an anti-inflammatory effect on carotid atherosclerosis in CKD patients by improving renal function, and ^{18}F-FDG PET/CT can be an assessment tool for atherosclerosis. These findings need further investigation to determine the long-term effects of renal transplantation on atherosclerosis.

Conflict of interest

None.

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