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Original Article

ORIGINAL ARTICLE

Cerebral blood flow following successful living kidney transplantation: the VINTAGE study

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ABSTRACT

Background. Chronic kidney disease (CKD) is a significant risk factor for cerebrovascular disease. However, there is limited research on how successful living donor kidney transplantation (LDKT) affects cerebral blood flow (CBF). This study aims to comprehensively investigate how LDKT influences CBF across various brain levels and regions.
Methods. Data from 53 recipients between 2016 and 2020 were obtained from the VINTAGE study conducted at our hospital. CBF was measured by level and region using single-photon emission computed tomography (SPECT), according to the Talairach brain atlas. The primary endpoint was the mean difference in CBF before and 1-year post-LDKT. Subgroup analysis using traditional risk factors assessed the heterogeneity of the effect on CBF in the frontal lobe region.
Results. LDKT improved blood flow in the anterior cerebral artery and middle cerebral artery but had less impact on the posterior cerebral artery. The most consistent improvements were observed in the frontal lobe region {left frontal lobe: −0.12 [95% confidence interval (CI) −0.18 to −0.05], $P < .001$; right frontal lobe: −0.13 [95% CI −0.21 to −0.05], $P = .001$}. Subgroup analysis showed a consistent effect of LDKT on frontal lobe CBF improvement, with no qualitative interaction observed.
Conclusions. LDKT contributes to the normalization of CBF, with improvement in anterior circulation and frontal lobe blood flow. To clarify the clinical significance of KT's CBF-improving effect, future studies should investigate the relationship between specific cognitive impairments (e.g. short-term memory, visuospatial ability, executive function) and CBF in each perfusion region.

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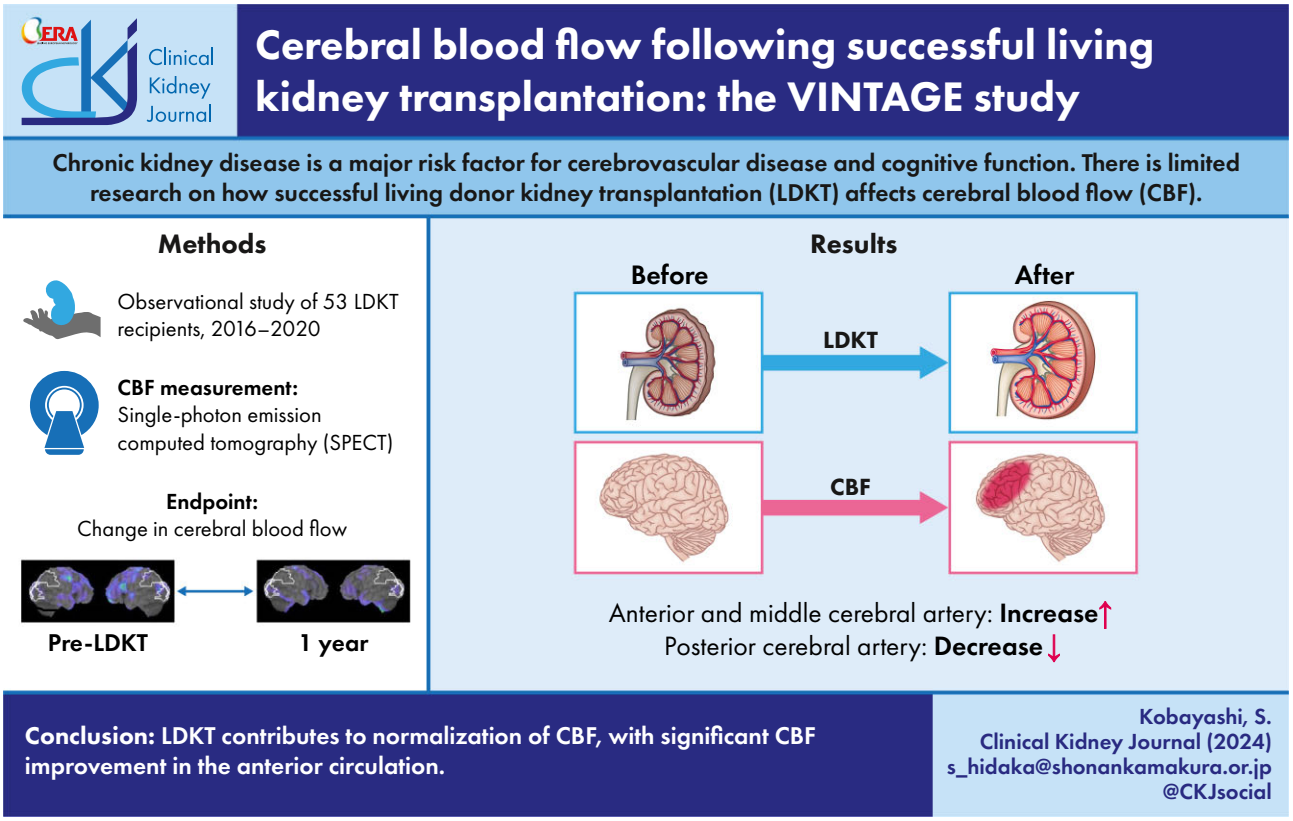
GRAPHICAL ABSTRACT



Keywords: cerebral blood flow, cognitive function, frontal lobe, kidney transplantation, single-photon emission computed tomography

KEY LEARNING POINTS

What was known:

- Dialysis patients have been shown to have reduced cerebral blood flow and cognitive function.
- Kidney transplantation (KT) has been shown to improve these conditions.
- There are limited studies that have comprehensively evaluated cerebral blood flow after KT.

This study adds:

- The effect of kidney transplantation on cerebral blood flow improvement was not necessarily homogeneous across all brain regions.
- Anterior cerebral blood flow improves with bilateral improvement to the frontal lobes.

Potential impact:

- In the future, by clarifying the relationship between the degree of each cognitive impairment and the CBF of each perfusion area, it may be possible to elucidate the clinical significance of the CBF-improving effect of KT.

INTRODUCTION

Chronic kidney disease (CKD) is a major independent risk factor for cerebrovascular disease [1–4]. Dialysis is associated with reduced cerebral blood flow (CBF), which may partly explain the high prevalence of stroke and cognitive impairment in dialysis patients [5]. According to the Japanese Society for Dialysis Therapy Renal Data Registry, the proportion of deaths due to cardiovascular disease in 2020 was 32.0% [6].

Kidney transplantation (KT) reduces the incidence of cerebrovascular events compared with dialysis [7, 8]. Also, previous reports show that KT improves cognitive function in dialysis patients. This suggests that KT contributes to improving CBF in the frontal lobe region [9, 10]. However, there are only a limited

number of studies that comprehensively and in detail examine the changes in CBF in kidney transplant recipients (KTRs) before and after KT, and it remains unclear whether KT improves CBF uniformly. The pathophysiology of the kidney–brain relationship remains a poorly understood area. Thus it has been noted that the possibility that cognitive decline after KT is partially reversible needs to be further empirically investigated [11].

This study aims to clarify detailed changes in CBF by level and region (Talairach brain atlas) before and after living donor kidney transplantation (LDKT). The primary endpoint is the mean difference in CBF before KT and after 1 year, as measured using quantitative single-photon emission computed tomography (SPECT).

MATERIALS AND METHODS

Study population

A total of 53 patients who underwent LDKT and SPECT from 2016 to 2020 were consecutively selected from the Visualizing the Pathophysiology of Kidney Transplantation in Modern Age (VINTAGE) study. Briefly, the VINTAGE study is an ongoing observational cohort study combining retrospective and prospective data conducted at the Kidney Disease and Transplant Center and the Kidney Transplant and Robotic Surgery Center of Shonan Kamakura General Hospital. This study was approved by the relevant ethics committee (approval number TGE02305-024) and conducted in accordance with the Declaration of Helsinki and the Declaration of Istanbul on Organ Trafficking and Transplant Tourism. Informed consent was obtained through an opt-out procedure, where KTRs were given the opportunity to opt out via an information sheet or the hospital website.

Immunosuppression and desensitization

Our regimen incorporates mycophenolate mofetil (MMF) and methylprednisolone (MP), with prolonged-release tacrolimus (PR-TAC) initiated 8 days pre-transplant at 0.10 mg/kg/day. Dose adjustments aim for trough levels of 8–10 ng/ml at the time of KT, 6–8 ng/ml for 1–2 months post-KT, then 4–5 ng/ml thereafter. MMF is initiated at 1500–2000 mg/day, 8 days pre-KT, and reduced to 1000–1500 mg/day postoperatively based on white blood cell count. MP starts at 20 mg/day, 8 days pre-KT, increases to 500 mg on surgery day, then tapers to 6-8 mg/day within 1–2 months post-KT. Basiliximab induction is administered on the day of surgery and postoperative day 4. Desensitization with rituximab and double filtration plasmapheresis may be considered for recipients with ABO/human leucocyte antigen (HLA) incompatibility or sensitization due to previous pregnancy, transplant or transfusion, based on individual clinical assessment.

^{123}I-IMP brain SPECT examination

The SPECT examination was performed approximately 4–7 days before KT. After intravenous injection of 185 MBq (5 mCi) of ^{123}I-IMP (iodoamphetamine) into the KTR, SPECT data were collected for 21 minutes starting 15 minutes after injection. The images were taken using a Siemens e.cam gamma camera (Siemens, Munich, Germany)[12].

Statistical brain image analysis

CBF in each brain region was assessed using three-dimensional stereotactic surface projection (3D-SSP) image analysis software (iSSP version 3.5, Medi-Physics, Tokyo, Japan) [13] and the stereotactic extraction estimation (SEE) method [14]. For 3D-SSP, following image reconstruction, pixel values from anatomically standardized KTR SPECT data were normalized to the whole-brain mean and compared with a similarly constructed normal database (NDB). A Z-score was calculated for each pixel as follows: Z-score = [(NDB mean) − (KTR data)]/[NDB standard deviation (SD)]. For SEE, anatomical information corresponding to brain coordinates was integrated with the Z-scores from the 3D-SSP to calculate regional Z-scores. As indicated by the Z-score formula, a Z-score of 1 signifies that the KTR's CBF is 1 SD lower than the normal mean. Higher Z-scores represent lower regional CBF in the KTR, while lower Z-scores indicate CBF within the normal range.

Primary endpoint

The primary outcome measure was the mean difference in CBF, i.e. the mean of (Z-score after 1 year) − (Z-score before KT), with negative values indicating improvement in CBF, zero indicating no change and positive values indicating deterioration.

Power and sample size analysis

Assuming a mean difference in CBF before and after KT of 0.1, an SD of 0.25, a pre–post correlation of 0.6, a significance level of 0.05 (two-sided) and a desired power of 80%, the minimum required sample size was 42. The actual power of this study, involving 53 KTRs, was 89%. Parameters for the sample size calculation were based on findings from our previous study [12].

Statistical analysis

Analyses were performed using SAS version 9.4 TS1M7 (SAS Institute, Cary, NC, USA). Data were summarized as frequencies, mean ± SD or median [interquartile range (IQR)]. Differences in changes in laboratory values were assessed using paired *t*-tests for normally distributed data and Wilcoxon signed-rank tests for skewed distributed data. Normality was assessed with the Shapiro–Wilk test. Point estimates of mean differences of regional CBF were displayed as forest plots with 95% confidence intervals (CIs) and *P*-values by paired *t*-tests. Subgroup analysis was performed based on medical history and comorbidities (traditional risk factors) to assess potential heterogeneity in the effect of KT on CBF. Student's unpaired *t*-test was used to examine the heterogeneity of CBF changes between subgroups. Equality of variance was assessed by the F test. A two-sided *P*-value $<.05$ was considered statistically significant. All analyses were performed by an independent data centre (STATZ Institute, Tokyo, Japan).

RESULTS

Characteristics of study participants

Table 1 summarizes the characteristics of the 53 KTRs. The mean age of recipients was 55 ± 12 years and the mean age of donors was 59 ± 11 years. Male recipients comprised 66% of the population, while female donors represented 60%. The median dialysis duration was 12 months, with 42% receiving pre-emptive KT. Spouses were the most common donor type. Diabetes was the most frequent underlying disease (32%). Included in the study were 7 KTRs (13%) with a previous diagnosis of stroke. One year after KT, the mean estimated glomerular

Table 1: Characteristics of study participants ($n = 53$).

Variables	Values	P-value
Recipient		
Age (years), mean ± SD	54.6 ± 12.4	
Men, *n* (%)	35 (66.0)	
Body mass index (kg/m^2), mean ± SD	23.4 ± 4.0	
Duration of dialysis (months), median (IQR)[a]	12 (2–29)	
Pre-emptive kidney transplant, *n* (%)	22 (41.5)	
Medical history, *n* (%)		
Peripheral arterial disease	5 (9.4)	
Ischaemic heart disease	11 (20.8)	
Arrhythmia	2 (3.8)	
Stroke	7 (13.2)	
Malignant tumour	9 (17.0)	
Comorbidities, *n* (%)		
Hypertension	45 (84.9)	
Diabetes	22 (41.5)	
Dyslipidaemia	25 (47.2)	
End-stage renal disease, *n* (%)		
Chronic glomerulonephritis	13 (24.5)	
Diabetes mellitus	17 (32.1)	
Autosomal dominant polycystic kidney disease	9 (17.0)	
Other	14 (26.4)	
Histocompatibility, *n* (%)		
HLA incompatible	4 (7.5)	
ABO incompatible	21 (39.6)	
Donor		
Age (years), mean ± SD	59.2 ± 10.9	
Women, *n* (%)	32 (60.4)	
Spouse donor, *n* (%)	33 (62.3)	
Overall rejection, *n* (%)	4 (7.5)	
eGFR (ml/min/1.73 m^2), mean ± SD		
Pre	6.1 ± 2.5	<.001
Post-1 year	42.8 ± 10.2	
Haemoglobin (g/dl), mean ± SD		
Pre	11.2 ± 1.3	<.001
Post-1 year	13.1 ± 1.8	
BUN (mg/dl), mean ± SD		
Pre	57.2 ± 16.4	<.001
Post-1 year	20.2 ± 5.5	
Systolic blood pressure (mmHg), mean ± SD		
Pre	140.3 ± 22.1	<.001
Post-1 year	125.3 ± 12.6	
Diastolic blood pressure (mmHg), mean ± SD		
Pre	82.5 ± 13.9	.002
Post-1 year	76.3 ± 9.5	
HbA1c (%), mean ± SD		
Pre	5.7 ± 0.9	.002
Post-1 year	6.1 ± 0.9	
Total cholesterol (mg/dl), mean ± SD		
Pre	171.5 ± 36.7	<.001
Post-1 year	207.9 ± 39.3	
Triglyceride (mg/dl), median (IQR)		
Pre	120 (72–189)	.030
Post-1 year	127 (92–200)]	

filtration rate (eGFR) and mean haemoglobin (Hb) increased to 42.8 ± 10.2 ml/min/1.73 m^2 and 13.1 ± 1.8 mg/dl, respectively. Mean blood urea nitrogen (BUN) decreased from 57.2 ± 16.4 to 20.2 ± 5.5 mg/dl. Compared with preoperative values, systolic blood pressure and diastolic blood pressure decreased, while HbA1c, total cholesterol and triglycerides increased.

Table 2: Immunosuppressant exposure levels.

Variables	Values
PR-TAC trough (ng/ml)	
Pre-KT SPECT	5.0 ± 2.3
Immediately before KT	12.9 ± 4.5
2 weeks	8.7 ± 2.5
1 month	8.3 ± 2.5
3 months	7.2 ± 1.7
6 months	5.5 ± 1.6
1 year	4.9 ± 2.0
PR-TAC dose (mg/kg/day)	
Immediately before KT	0.11 ± 0.05
2 weeks	0.13 ± 0.06
1 month	0.11 ± 0.05
3 months	0.10 ± 0.04
6 months	0.07 ± 0.04
1 year	0.06 ± 0.03
MMF dose (mg/day)	
Immediately before KT	1906 ± 241
2 weeks	1561 ± 298
1 month	1448 ± 296
3 months	1189 ± 416
6 months	1074 ± 425
1 years	950 ± 466
MP dose (mg/day)	
Immediately before KT	500.0 ± 0.0
2 weeks	8.2 ± 1.1
1 month	7.8 ± 0.7
3 months	6.8 ± 1.9
6 months	4.2 ± 1.1
1 year	3.6 ± 0.8

If pre-KT trough levels were not measured on the day of the SPECT examination, the closest available measurement to that time point was used. There was no significant difference in TAC trough levels at the time of SPECT pre- and post-KT (5.0 ± 2.3 versus 4.9 ± 2.0 ng/ml; $P = .912$).

Immunosuppressant exposure levels

Table 2 shows the 1-year use of immunosuppressants, demonstrating a tapering trend over time for all agents. There was no significant difference in TAC trough levels at the time of SPECT pre- and post-KT (5.0 ± 2.3 versus 4.9 ± 2.0 ng/ml; $P = .912$). The mean PR-TAC trough level decreased from 12.9 ± 4.5 ng/ml immediately before KT to 4.9 ± 2.0 ng/ml 1 year post-KT.

Overview of blood flow changes in cerebral arteries

Figure 1 highlights changes in mean CBF across three cerebral arteries. The posterior cerebral artery (PCA), via the vertebral artery, showed a bilateral decrease in CBF. The anterior cerebral artery (ACA) and middle cerebral artery (MCA), via the internal carotid artery, showed an increase. Before KT, CBF was higher on the left side for all three arteries, with slopes of change from pre- to post-KT being similar for both hemispheres. The right MCA was most severe pre-KT and the left PCA was mildest. The ACA showed no left–right differences.

Mean CBF changes by level and region

Figures 2 and 3 illustrate detailed CBF changes by level and region for the left and right hemispheres, respectively. Among the three cerebral arteries, ACA had the greatest improvement in CBF [left ACA: −0.09 (95% CI −0.17 to −0.02), $P = .014$; right ACA: −0.09 (95% CI −0.17 to −0.01), $P = .02$]. Also, definitive improvements in frontal lobe region were observed bilaterally

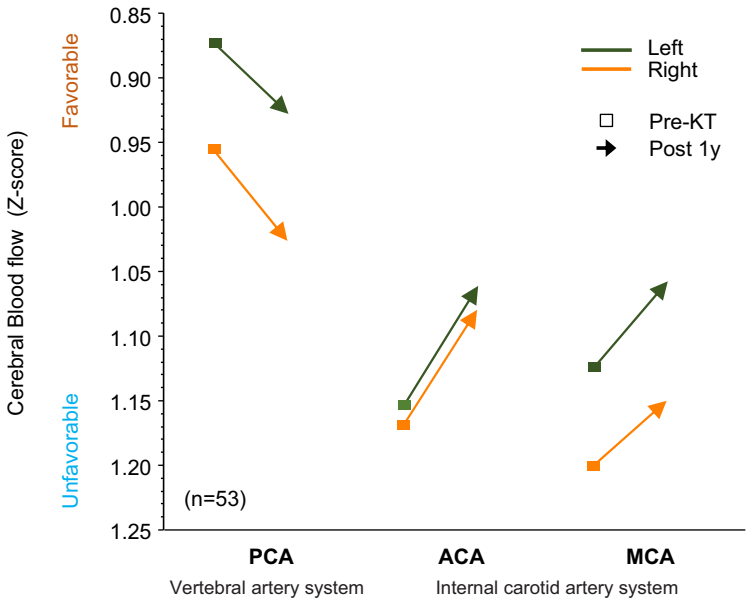


Figure 1: Overview of blood flow changes in cerebral arteries. A lower Z-score indicates higher CBF, whereas a higher Z-score indicates lower CBF.

with a narrow 95% CI [left frontal lobe: −0.12 (95% CI −0.18 to −0.05), $P < .001$; right frontal lobe: −0.13 (95% CI −0.21 to −0.05), $P = .001$].

Subgroup analyses of CBF changes in the frontal lobe

Subgroup analysis using traditional risk factors revealed no statistical heterogeneity in the positive effect of KT on CBF in the frontal lobe, suggesting a consistent benefit (Fig. 4).

DISCUSSION

This study demonstrated that among the three major cerebral arteries, LDKT improved blood flow in the ACA and MCA but had a less pronounced effect on the PCA (Fig. 1). Moreover, detailed exploratory and subgroup analyses revealed consistent improvements in CBF within the frontal lobe region (Figs. 2–4).

The ACA and MCA are supplied by the internal carotid artery, while the PCA receives blood flow from the vertebral artery (VA), each with distinct perfusion territories. Previous research has shown that under hypoxic conditions, the relative increase in VA blood flow is 50% greater than in other vessels, suggesting differential regulation of blood flow to the brainstem and cortex [15, 16]. This discrepancy in blood flow regulation may explain our findings (Fig. 1), where KT improved CBF in the ACA and MCA but had less impact on the PCA, which exhibited relatively good CBF pre-transplant. This suggests that KT may normalize CBF across cerebral arteries by mitigating the relative increase in PCA blood flow.

In this study, no difference was found in TAC trough levels at the time of SPECT examinations before and after KT (Table 2). It is noteworthy that calcineurin inhibitors such as TAC can cause endothelial dysfunction and have vasoconstrictor effects. Interestingly, in their pilot study, Tariq *et al.* [17] reported that reducing TAC trough levels may improve CBF, particularly in the frontal and parietal regions.

Hb levels improved post-KT (Table 1). While Molnar *et al.* [18] demonstrated a significantly higher mortality rate in anaemic versus non-anaemic groups, several reports have noted an inverse correlation between CBF and Hb level [19]. Although cardiorenal anaemia syndrome is well recognized [20], the relationship between Hb and brain function in CKD, particularly in KTRs, remains poorly understood and warrants further investigation. At present, we cannot exclude the possibility that improvement in Hb levels may be one of the mechanisms underlying improvement in CBF.

The marked decrease in BUN following KT may have contributed to the observed CBF improvement (Table 1). Of note, the improvement in CBF was more pronounced in KTRs with higher BUN levels than in those with lower BUN levels (Fig. 4), suggesting a contribution from the reduction in non-protein nitrogens. Matsuki *et al.* [21] demonstrated that elevated blood urea, a consequence of kidney disease, activates matrix metalloproteinase 2, which is implicated in blood–brain barrier dysfunction and increased brain permeability. Their findings suggest that the accumulation of urea and other uraemic toxins, beyond the simple filtration function of the kidneys, may contribute to cognitive decline. Additionally, while we have not yet measured protein-bound uraemic toxins like indoxyl sulphate, p-cresyl sulphate and phenyl sulphate in the stored samples, their potential role cannot be dismissed. These toxins, incompletely removed by haemodialysis, may contribute to CBF impairment, and their reduction following KT may also play a part in the observed CBF improvements [22].

Dialysis patients are exposed to metabolic derangements, chronic inflammation and oxidative stress, in addition to traditional cardiovascular risk factors. KT has been shown to effectively reduce oxidative stress, thereby mitigating CVD morbidity and mortality through mechanisms such as modifying immunologic responses, improving endothelial function, inhibiting platelet aggregation and reducing arteriosclerosis [23].

KT has been associated with improvements in cardiac structure and function, specifically reverse cardiac remodelling [24], and improved CBF has also been reported following heart transplantation [25]. From a haemodynamic perspective, it is plausible that the observed improvement in CBF after KT is

Level		Cerebral blood flow (Z-score) Pre	Post 1y	Mean difference (95% confidence interval)	P-value
0	PCA	0.87±0.40	0.93±0.44	0.05 (-0.02 to 0.13)	0.169
	ACA	1.15±0.30	1.06±0.29	-0.09 (-0.17 to -0.02)	0.014
	MCA	1.12±0.21	1.06±0.27	-0.07 (-0.13 to 0.00)	0.037
1	Cerebellum	0.60±0.32	0.65±0.40	0.05 (-0.04 to 0.14)	0.239
	Cerebrum	1.12±0.20	1.06±0.24	-0.05 (-0.10 to 0.00)	0.041
	Brainstem	0.49±0.26	0.50±0.34	0.01 (-0.13 to 0.14)	0.926
2	Pons	0.44±0.24	0.50±0.36	0.09 (-0.05 to 0.24)	0.208
	Occipital Lobe	0.87±0.42	0.92±0.49	0.05 (-0.05 to 0.14)	0.329
	Posterior Lobe	0.59±0.33	0.66±0.40	0.06 (-0.03 to 0.16)	0.177
	Frontal Lobe	1.16±0.26	1.05±0.26	-0.12 (-0.18 to -0.05)	<.001
	Anterior Lobe	0.58±0.43	0.57±0.47	-0.02 (-0.17 to 0.14)	0.841
	Temporal Lobe	0.90±0.29	0.89±0.39	-0.02 (-0.10 to 0.07)	0.705
	Limbic Lobe	0.88±0.30	0.89±0.32	0.01 (-0.06 to 0.08)	0.747
	Midbrain	0.48±0.28	0.53±0.41	0.10 (-0.14 to 0.33)	0.399
	Parietal Lobe	1.15±0.34	1.10±0.39	-0.06 (-0.13 to 0.02)	0.131
3	Supramarginal Gyrus	0.98±0.59	0.89±0.59	-0.09 (-0.29 to 0.11)	0.352
	Transverse Temporal Gyrus	0.99±0.81	0.71±0.61	-0.42 (-0.67 to -0.17)	0.002
	Inferior Occipital Gyrus	0.52±0.46	0.69±0.58	0.23 (0.05 to 0.41)	0.015
	Inferior Frontal Gyrus	0.75±0.45	0.63±0.36	-0.13 (-0.24 to -0.03)	0.014
	Inferior Temporal Gyrus	0.75±0.31	0.77±0.42	0.05 (-0.05 to 0.14)	0.326
	Inferior Parietal Lobule	1.14±0.46	1.05±0.59	-0.09 (-0.22 to 0.03)	0.148
	Angular Gyrus	0.98±0.59	1.03±0.66	0.02 (-0.18 to 0.22)	0.852
	Orbital Gyrus	0.64±0.63	0.60±0.47	-0.12 (-0.36 to 0.12)	0.305
	Posterior Cingulate	0.73±0.37	0.72±0.39	0.00 (-0.11 to 0.11)	0.994
	Thalamus	0.42±0.35	0.56±0.54	0.18 (-0.17 to 0.52)	0.294
	Superior Occipital Gyrus	0.73±0.59	0.83±0.61	0.08 (-0.16 to 0.31)	0.518
	Superior Frontal Gyrus	1.25±0.34	1.13±0.34	-0.12 (-0.23 to -0.02)	0.022
	Superior Temporal Gyrus	0.90±0.35	0.87±0.43	-0.03 (-0.13 to 0.08)	0.595
	Superior Parietal Lobule	0.99±0.53	1.00±0.50	0.00 (-0.11 to 0.10)	0.961
	Lingual Gyrus	0.87±0.65	0.94±0.65	0.08 (-0.10 to 0.25)	0.379
	Anterior Cingulate	0.55±0.31	0.54±0.36	-0.01 (-0.08 to 0.06)	0.771
	Cingulate Gyrus	0.97±0.38	0.98±0.41	0.01 (-0.09 to 0.11)	0.791
	Middle Occipital Gyrus	0.70±0.41	0.79±0.57	0.10 (-0.03 to 0.22)	0.140
	Postcentral Gyrus	1.19±0.43	1.08±0.41	-0.11 (-0.21 to -0.01)	0.026
	Precentral Gyrus	1.32±0.39	1.23±0.34	-0.09 (-0.19 to 0.01)	0.079
	Middle Frontal Gyrus	1.09±0.33	0.95±0.34	-0.14 (-0.23 to -0.06)	<.001
	Middle Temporal Gyrus	0.92±0.37	0.94±0.49	0.01 (-0.11 to 0.13)	0.888
	Rectal Gyrus	0.47±0.35	0.55±0.40	0.11 (-0.19 to 0.42)	0.438
	Medial Frontal Gyrus	1.09±0.34	0.98±0.34	-0.11 (-0.19 to -0.02)	0.015
	Parahippocampal Gyrus	0.24±0.15	0.58±0.47	0.30 (-0.14 to 0.75)	0.153
	Paracentral Lobule	1.03±0.57	0.96±0.54	-0.11 (-0.22 to 0.00)	0.042
	Fusiform Gyrus	0.64±0.37	0.63±0.32	0.01 (-0.10 to 0.12)	0.867
	Subcallosal Gyrus	0.34±0.33	0.55±0.58	0.28 (-0.23 to 0.78)	0.252
	Precuneus	1.08±0.54	1.04±0.64	-0.04 (-0.17 to 0.10)	0.592
	Cuneus	0.91±0.51	1.00±0.58	0.08 (-0.02 to 0.18)	0.099
	Uncus	0.39±0.22	0.45±0.28	0.01 (-0.19 to 0.21)	0.935

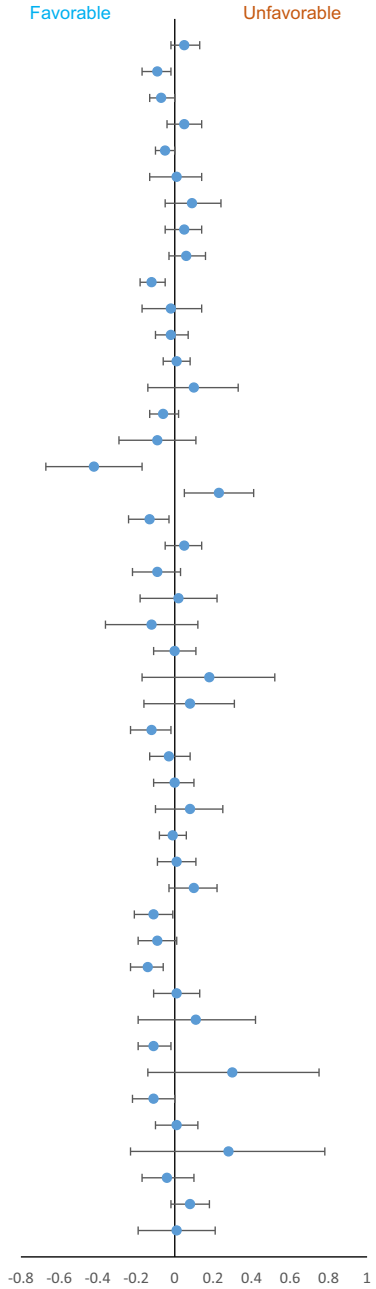


Figure 2: Left-side mean CBF changes by level and region. Levels and areas follow the Talairach brain atlas. A negative mean difference indicates improvement in CBF, zero indicates no change and positive indicates deterioration. Light blue indicates areas that showed favourable effects and brown indicates areas that showed unfavourable effects.

mediated, at least in part, by improved cardiac function. Cardiorenal syndrome type 4, or 'chronic renocardiac syndrome', is characterized by CKD as the primary condition leading to decreased cardiac function, ventricular hypertrophy, diastolic dysfunction and an increased risk of adverse CVD events [26, 27]. Ventricular remodelling is well-documented in CKD patients [28], and severe chronic heart failure has been linked to ≈30% reductions in CBF. While further research is needed to confirm this concept, our findings may point towards a new conceptual framework, the 'cerebro-cardio-renal syndrome', with potential implications for the clinical management of CKD patients.

Furthermore, it is important to acknowledge that our findings and interpretations are limited to information readily accessible in routine clinical practice. While factors such as carbon dioxide, H^+ concentration, oxygen concentration and astrocyte secretions are known to influence CBF physiologically, the actual CBF dynamics in CKD patients are complex. Secondary

Level		Cerebral blood flow (Z-score) Pre	Post 1y	Mean difference (95% confidence interval)	P-value
0	PCA	0.96±0.36	1.03±0.47	0.07 (-0.02 to 0.15)	0.107
	ACA	1.17±0.28	1.08±0.26	-0.09 (-0.17 to -0.01)	0.020
	MCA	1.20±0.25	1.15±0.27	-0.05 (-0.12 to 0.01)	0.126
1	Cerebellum	0.69±0.34	0.73±0.44	0.04 (-0.07 to 0.15)	0.490
	Cerebrum	1.17±0.19	1.13±0.22	-0.04 (-0.09 to 0.02)	0.154
	Brainstem	0.51±0.35	0.54±0.32	0.01 (-0.16 to 0.17)	0.917
2	Pons	0.50±0.37	0.54±0.38	0.02 (-0.15 to 0.20)	0.782
	Occipital Lobe	0.91±0.39	1.01±0.52	0.11 (0.00 to 0.21)	0.043
	Posterior Lobe	0.68±0.34	0.73±0.44	0.04 (-0.07 to 0.16)	0.449
	Frontal Lobe	1.22±0.28	1.09±0.26	-0.13 (-0.21 to -0.05)	0.001
	Anterior Lobe	0.55±0.42	0.58±0.47	0.04 (-0.09 to 0.18)	0.512
	Temporal Lobe	1.01±0.33	1.05±0.37	0.04 (-0.04 to 0.13)	0.313
	Limbic Lobe	0.91±0.30	0.92±0.34	0.01 (-0.06 to 0.08)	0.780
	Midbrain	0.51±0.44	0.51±0.36	0.06 (-0.25 to 0.36)	0.695
	Parietal Lobe	1.23±0.34	1.15±0.40	-0.08 (-0.16 to 0.01)	0.066
3	Supramarginal Gyrus	1.31±0.82	1.35±0.72	-0.01 (-0.24 to 0.23)	0.940
	Transverse Temporal Gyrus	1.23±0.89	1.16±0.99	-0.07 (-0.38 to 0.24)	0.651
	Inferior Occipital Gyrus	0.69±0.50	0.80±0.63	0.13 (-0.06 to 0.33)	0.169
	Inferior Frontal Gyrus	1.03±0.50	0.94±0.49	-0.10 (-0.25 to 0.05)	0.190
	Inferior Temporal Gyrus	0.85±0.39	0.95±0.39	0.09 (-0.03 to 0.22)	0.139
	Inferior Parietal Lobule	1.36±0.51	1.22±0.59	-0.14 (-0.30 to 0.01)	0.068
	Angular Gyrus	0.84±0.50	0.95±0.56	0.09 (-0.07 to 0.24)	0.258
	Orbital Gyrus	0.72±0.67	0.60±0.65	-0.17 (-0.46 to 0.12)	0.226
	Posterior Cingulate	0.74±0.40	0.79±0.46	0.05 (-0.07 to 0.17)	0.390
	Thalamus	0.75±0.53	0.67±0.50	-0.01 (-0.31 to 0.28)	0.918
	Superior Occipital Gyrus	0.69±0.49	0.82±0.60	0.15 (-0.04 to 0.35)	0.121
	Superior Frontal Gyrus	1.25±0.39	1.14±0.35	-0.11 (-0.23 to 0.01)	0.062
	Superior Temporal Gyrus	1.09±0.48	1.06±0.51	-0.04 (-0.15 to 0.08)	0.519
	Superior Parietal Lobule	1.03±0.40	0.98±0.57	-0.06 (-0.17 to 0.06)	0.357
	Lingual Gyrus	0.70±0.51	0.75±0.67	0.05 (-0.09 to 0.19)	0.466
	Anterior Cingulate	0.61±0.32	0.57±0.36	-0.05 (-0.14 to 0.04)	0.255
	Cingulate Gyrus	0.99±0.36	0.99±0.37	0.00 (-0.08 to 0.08)	0.988
	Middle Occipital Gyrus	0.66±0.36	0.88±0.45	0.19 (0.06 to 0.32)	0.005
	Postcentral Gyrus	1.18±0.42	1.11±0.45	-0.07 (-0.18 to 0.03)	0.169
	Precentral Gyrus	1.13±0.41	1.04±0.36	-0.09 (-0.20 to 0.02)	0.099
	Middle Frontal Gyrus	1.28±0.43	1.09±0.35	-0.19 (-0.29 to -0.09)	<.001
	Middle Temporal Gyrus	0.98±0.37	1.01±0.42	0.03 (-0.08 to 0.14)	0.559
	Rectal Gyrus	0.49±0.50	0.47±0.36	-0.05 (-0.29 to 0.19)	0.661
	Medial Frontal Gyrus	1.15±0.35	1.01±0.32	-0.14 (-0.22 to -0.06)	0.001
	Parahippocampal Gyrus	0.38±0.31	0.49±0.41	0.11 (-0.12 to 0.33)	0.317
	Paracentral Lobule	0.96±0.53	0.88±0.52	-0.10 (-0.19 to -0.01)	0.036
	Fusiform Gyrus	0.76±0.31	0.84±0.37	0.07 (-0.04 to 0.18)	0.225
	Subcallosal Gyrus	0.50±0.53	0.58±0.55	0.18 (-0.28 to 0.64)	0.398
	Precuneus	1.13±0.61	1.07±0.64	-0.08 (-0.21 to 0.05)	0.245
	Cuneus	1.03±0.50	1.18±0.69	0.15 (0.00 to 0.30)	0.047
	Uncus	0.49±0.41	0.41±0.32	-0.10 (-0.38 to 0.18)	0.470

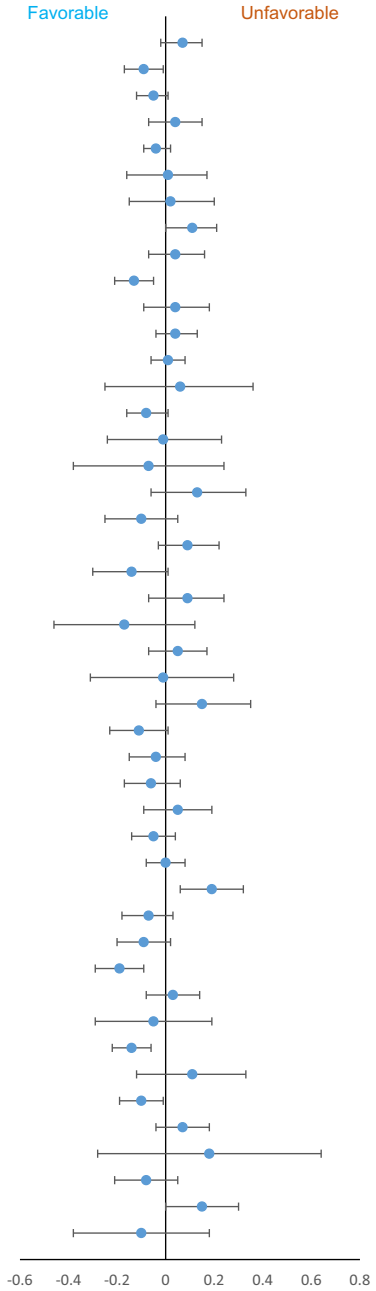


Figure 3: Right-side mean CBF changes by level and region. Levels and areas follow the Talairach brain atlas. A negative mean difference indicates improvement in CBF, zero indicates no change and positive indicates deterioration. Light blue indicates areas that showed favourable effects and brown indicates areas that showed unfavourable effects.

hyperparathyroidism, an overactive renin–angiotensin–aldosterone system, autoregulation and the prevalence of cerebral atherosclerotic sites, among other factors, may also play significant roles [24, 29, 30, 31].

Our results align with previous reports, further supporting and strengthening their findings. Findlay *et al.* [9] observed that patients who remained on dialysis without undergoing KT exhibited progressive lobar atrophy in the frontal, parietal and temporal lobes, with greater frontal atrophy correlating with worsening global cognitive and executive function scores. Similarly, Lepping *et al.* [32] demonstrated that KT can normalize abnormalities in CBF, neurochemical concentrations and white matter integrity in CKD patients.

This study has several limitations. A lack of cognitive function data precludes direct correlation analysis between CBF and cognitive outcomes. The absence of a control group makes attributing observed CBF changes solely to KT challenging without a comparison group. We used an observational study design,

	No. of recipient	Cerebral blood flow (Z-score) Mean Difference	(95% confidence interval)	P-value for heterogeneity
Left side			Favorable Unfavorable	
Age, year				
<60	32	-0.11	(-0.20 to -0.02)	0.92
≥60	21	-0.12	(-0.21 to -0.03)	
Sex				
Women	18	-0.09	(-0.22 to 0.04)	0.58
Men	35	-0.13	(-0.20 to -0.05)	
Obesity				
No	39	-0.13	(-0.21 to -0.05)	0.35
Yes	14	-0.06	(-0.17 to 0.04)	
Duration of dialysis, mo				
<12 or PKT	34	-0.14	(-0.20 to -0.08)	0.29
≥12	19	-0.07	(-0.21 to 0.07)	
Anemia				
No	7	-0.21	(-0.43 to 0.01)	0.30
Yes	46	-0.10	(-0.17 to -0.03)	
BUN				
<57,mg/dL	27	-0.07	(-0.16 to 0.02)	0.19
≥57,mg/dL	26	-0.16	(-0.25 to -0.06)	
Hypertension				
No	8	-0.04	(-0.18 to 0.11)	0.30
Yes	45	-0.13	(-0.20 to -0.06)	
Hyperlipidemia				
No	28	-0.09	(-0.19 to 0.01)	0.42
Yes	25	-0.14	(-0.22 to -0.07)	
Diabetes				
No	31	-0.10	(-0.19 to -0.02)	0.69
Yes	22	-0.13	(-0.23 to -0.03)	
PAD				
No	48	-0.11	(-0.17 to -0.05)	0.59
Yes	5	-0.17	(-0.64 to 0.30)	
IHD				
No	42	-0.11	(-0.19 to -0.04)	0.86
Yes	11	-0.13	(-0.27 to 0.02)	
Stroke				
No	46	-0.13	(-0.20 to -0.06)	0.19
Yes	7	-0.01	(-0.13 to 0.12)	
Right side				
Age, year				
<60	32	-0.14	(-0.25 to -0.02)	0.83
≥60	21	-0.12	(-0.21 to -0.03)	
Sex				
Women	18	-0.08	(-0.27 to 0.11)	0.32
Men	35	-0.16	(-0.23 to -0.09)	
Obesity				
No	39	-0.13	(-0.23 to -0.03)	0.99
Yes	14	-0.13	(-0.26 to 0.00)	
Duration of dialysis, mo				
<12 or PKT	34	-0.12	(-0.20 to -0.04)	0.74
≥12	19	-0.15	(-0.32 to 0.02)	
Anemia				
No	7	-0.26	(-0.49 to -0.02)	0.21
Yes	46	-0.11	(-0.19 to -0.03)	
BUN				
<57,mg/dL	27	-0.10	(-0.18 to -0.02)	0.42
≥57,mg/dL	26	-0.16	(-0.29 to -0.03)	
Hypertension				
No	8	-0.05	(-0.19 to 0.09)	0.38
Yes	45	-0.14	(-0.23 to -0.06)	
Hyperlipidemia				
No	28	-0.13	(-0.25 to -0.01)	0.91
Yes	25	-0.14	(-0.24 to -0.04)	
Diabetes				
No	31	-0.13	(-0.25 to -0.02)	0.89
Yes	22	-0.12	(-0.23 to -0.02)	
PAD				
No	48	-0.12	(-0.20 to -0.04)	0.42
Yes	5	-0.23	(-0.60 to 0.15)	
IHD				
No	42	-0.13	(-0.22 to -0.05)	0.85
Yes	11	-0.12	(-0.30 to 0.06)	
Stroke				
No	46	-0.14	(-0.22 to -0.05)	0.68
Yes	7	-0.09	(-0.27 to 0.09)	

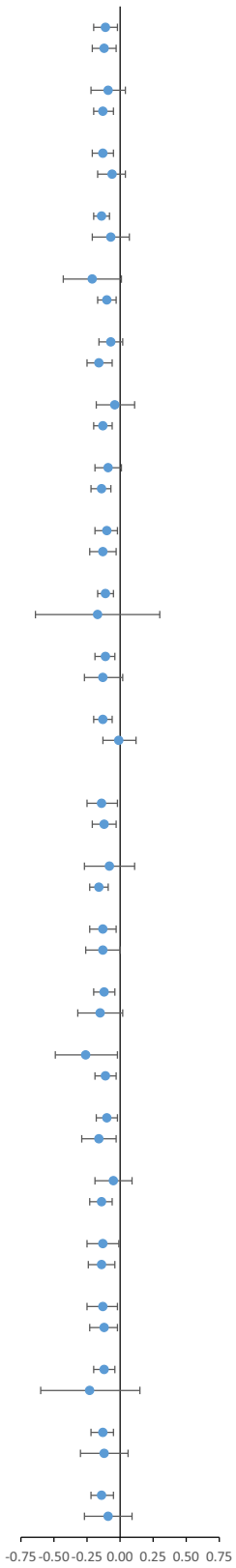


Figure 4: Subgroup analyses of CBF changes in the frontal lobe. PKT: pre-emptive kidney transplantation; PAD: peripheral arterial disease; IHD: ischaemic heart disease. Obesity is defined as a body mass index ≥25 kg/m^2 and anaemia is defined as haemoglobin levels <12.0 g/dl in women and <13.0 g/dl in men. This study was not designed to provide robust interval estimates for each stratum of subgroup factors. The 95% CI estimates for subgroup analysis are affected by the reduction in the number of cases and should be interpreted with caution.

thus if pre-KT trough levels were not measured on the day of the SPECT examination, the closest available measurement to that time point was used. Although no qualitative heterogeneity was detected in the frontal CBF subgroup analysis, sample size calculations based on statistical power for subgroup analyses are inherently difficult. CBF measurements were limited to KTRs without graft failure or death within 1 year, potentially skewing the results (immortal bias). To avoid creating a younger cohort, we did not exclude KTRs with a history of cerebrovascular disease. However, regional and racial variations in stroke risk among CKD patients may influence the findings [30, 33]. Additionally, the study's focus on LDKT recipients with relatively short dialysis duration and a higher rate of pre-emptive LDKT may limit the generalizability of the results.

Despite these limitations, this study remains valuable as one of the few to comprehensively and meticulously investigate the relationship between KT and CBF. Its strength lies in providing a detailed assessment of KT's impact on CBF improvement across various cerebral arteries, stratified by level and region. Future studies should aim to clarify the relationship between specific cognitive impairments (such as short-term memory, visuospatial ability and executive function) and CBF in each perfusion area, to better elucidate the clinical significance of KT's CBF-enhancing effect [34].

In conclusion, LDKT contributes to the normalization of CBF, with improvement in anterior circulation and frontal lobe blood flow. However, the precise mechanisms underlying LDKT's impact on CBF remain to be fully elucidated. Further research is warranted to investigate these mechanisms and their potential clinical implications.

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AUTHORS' CONTRIBUTIONS

S.K. was responsible for conceptualization, project administration and review and editing. S.H. was responsible for the methodology, original draft preparation, supervision and validation. K.T. was responsible for review and editing. The VINTAGE investigators were responsible for the investigation, data curation, software and formal analysis.

DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

APPENDIX

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