Received: 28 February 2024 | Revised: 22 May 2024 | Accepted: 1 June 2024

DOI: 10.1002/dad2.12614

Alzheimer's & Dementia
Diagnosis, Assessment & Disease Monitoring

RESEARCH ARTICLE

Changes in Alzheimer's disease blood biomarkers in kidney failure before and after kidney transplant

Anneka E. Blankenship[1,2] | **Lauren Yoksh**[3] | **Paul J. Kueck**[1,2] | **Jonathan D. Mahnken**[1,3,4] | **Jill K. Morris**[1,2] | **Aditi Gupta**[1,2,4,5]

[1]University of Kansas Alzheimer's Disease Research Center, University of Kansas Medical Center, Fairway, Kansas, USA

[2]Department of Neurology, University of Kansas Medical Center, Kansas City, Kansas, USA

[3]Department of Biostatistics & Data Science, University of Kansas Medical Center, Kansas City, Kansas, USA

[4]Frontiers Clinical & Translational Science Institute, University of Kansas Medical Center, Fairway, Kansas, USA

[5]Division of Nephrology and Hypertension, Department of Internal Medicine, University of Kansas Medical Center, Kansas City, Kansas, USA

Correspondence
Aditi Gupta, Associate Director, Frontiers Clinical & Translational Science Institute at the University of Kansas, Director, Internal Medicine Residency Research, Medical Director, Hoglund Biomedical Imaging Center, Director, Clinical Trials, Division of Nephrology and Hypertension, Department of Internal Medicine and Department of Neurology, University of Kansas Medical Center, 3901 Rainbow Blvd, Kansas City, KS 66160, USA.
Email: agupta@kumc.edu

Funding information
National Institutes of Health, Grant/Award Number: K23 AG055666; Kidney Institute Pilot, Grant/Award Numbers: R01AG062548, R01AG081304, P30 AG035982; University of Kansas Alzheimer's Disease Center, Grant/Award Number: UL1TR002366; University of Kansas for Frontiers CTSA

Abstract

INTRODUCTION: Alzheimer's disease (AD) blood biomarkers show promise for clinical diagnosis but their reliability in chronic kidney disease (CKD) is debated. This study investigates the impact of kidney transplant (KT) on AD biomarkers in CKD.

METHODS: We assessed AD biomarkers in 46 CKD patients pre-KT, at 12 weeks and 12 months post-KT, with baseline measures from 13 non-CKD controls. Using linear mixed models, we examined associations with participant groups, estimated glomerular filtration rate (eGFR) and cognition.

RESULTS: CKD patients showed elevated levels of neurofilament light (117 ± 72 vs. 11 ± 5 pg/mL), phosphorylated tau 181 (75 ± 42 vs. 13 ± 8 pg/mL), glial fibrillary acidic protein (193 ± 127 vs. 94 ± 39 pg/mL), amyloid β 42 (17 ± 5 vs. 5 ± 1 pg/mL), and amyloid β 40 (259 ± 96 vs. 72 ± 17 pg/mL) compared to controls. Post-KT, biomarker levels approached normal with improved eGFR, paralleled by enhanced cognitive function.

DISCUSSION: AD blood biomarker elevations in CKD are reversible with improved kidney function through KT.

KEYWORDS
Alzheimer's disease, amyloid beta, biomarkers, chronic kidney disease, cognition, estimated glomerular filtration, glial fibrillary acidic protein, kidney transplant, neurofilament light, phosphorylated tau, vascular dementia

Highlights

- AD biomarker levels are extremely high in severe CKD.
- AD biomarker levels are higher in patients with kidney failure on dialysis when compared to CKD patients not on dialysis.
- These elevations in AD biomarker levels in kidney failure are reversable and decrease dramatically after kidney transplantation.
- The change in biomarker levels after transplantation align with changes in kidney function.

- The change in biomarker levels after transplantation align with changes in cognitive function.

1 | BACKGROUND

Alzheimer's disease (AD) affects an estimated 55 million individuals and is poised to escalate to 139 million by 2050.[1] Urgent efforts are needed to understand the multifaceted nature of AD and develop tools for early diagnosis and prognostication. In this context, blood-based biomarkers such as, neurofilament light (NfL), phosphorylated tau (p-Tau), glial fibrillary acidic protein (GFAP), amyloid β 42 (Aβ42), and amyloid β 40 (Aβ40) have emerged as valuable noninvasive, cost-effective, and infrastructure-efficient tools for early detection and risk assessment for AD.[2]

Despite the increasing availability of these biomarkers and keen interest in implementing their use in clinical practice, their lack of generalizability remains challenging.[3] Before their widespread implementation, it is important to validate these biomarkers in different populations and medical comorbidities. Chronic kidney disease (CKD), an independent risk factor for cognitive impairment and dementia[4,5] affects the levels of AD blood biomarkers. Reduced kidney function or estimated glomerular filtration rate (eGFR) may increase the levels of these biomarkers.[6–14] As the significance of AD biomarker research grows, understanding the impact of kidney function on these biomarkers becomes critical for accurate result interpretation and establishing robust reference ranges.

The relationship between eGFR and AD biomarkers is complex, with unclear mechanistic links. Reduced kidney function can potentially alter the clearance of biomarkers.[15–17] If this is the case, then restoring kidney function should lower the blood biomarker values. Conversely, since CKD is a risk factor for dementia, the increased blood biomarker levels in CKD may be a marker for AD burden. However, the reliability of the biomarkers may not be the same in CKD as in the general population due to the role of the kidneys in their elimination.[10] Thus, in either case, CKD may alter a biomarker's normal reference range, necessitating additional consideration in clinical screening and diagnosis.

In this study, we explore the association between kidney function and AD blood biomarkers further. Specifically, we investigate changes in AD blood biomarkers before and after kidney transplantation, a novel approach that has not been previously explored. By investigating biomarker level changes with transplantation and their association with eGFR and cognitive performance, the study aims to provide valuable insights to clinical interpretations of these biomarkers in CKD. Indeed, CKD affects almost half the population > 70 years of age; an age group at risk of AD.[18] As the pursuit of effective dementia management intensifies, unraveling the intricacies of CKD's influence on blood biomarkers becomes paramount for advancing the clinical utility of these promising diagnostic tools for AD.

2 | METHODS

2.1 | Study design

We conducted a single center prospective longitudinal observational cohort study of patients with CKD undergoing kidney transplantation, where we studied the changes in AD blood biomarkers before and after kidney transplant, and their association with cognitive function. Patients with CKD who were on the kidney transplant list were enrolled and followed longitudinally until 1 year after their transplant. Control participants without CKD or cognitive impairment were also enrolled for comparison. The study was approved by the institutional review board (Institutional Organization # IORG0000100) and all participants signed an informed consent.

2.2 | Study participants

Adult patients with kidney failure who were on the kidney transplant waitlist and expected to receive a kidney transplant within 1 year were enrolled. These included patients scheduled for a living donor kidney transplant, listed for kidney transplant for at least 2 years, or backups for recent organ offers. Exclusion criteria included multi-organ listing, recent stroke, uncontrolled psychosis, active seizure disorder, or current use of antipsychotics. We also included a control group comprised of study participants of similar age (mean age 50.7 years vs. 51.9 years in the CKD group, see results) but without CKD, subjective complaints of memory loss, clinical diagnosis of mild cognitive impairment or dementia, or other concerns about cognitive function. The control group underwent a single study visit where demographic and clinical information was obtained, a blood sample was collected, and cognitive function was assessed.

CKD patients were followed for up to 12 months post-kidney transplant. We examined pre- and post-kidney transplant AD blood biomarker levels, eGFR, and cognitive function and compared our findings to the control group without CKD or AD. Study visits were conducted at baseline (pre-transplant), 12 weeks post-transplant, and 12 months post-transplant. If it had been 1 year since the baseline evaluation and the patient had still not received a kidney transplant, then a second pre-transplant visit was scheduled, and data from this more proximal visit to the kidney transplant were used for the pre-transplant assessment in our analyses. Thus, the time between the pre-transplant assessment and kidney transplant is always less than 1 year.

2.3 | Demographic and clinical data

Demographic and clinical data, including age, race, and ethnicity (self-identified), sex, level of education, and medical history, were obtained through medical records. If any information was missing or not clear in the medical records, the study coordinator clarified the information with the participant.

2.4 | Alzheimer's disease blood biomarker analysis

For patients with CKD, we collected blood samples before the kidney transplant, 12 weeks post-kidney transplant, and 12 months post-kidney transplant. For patients on in-center hemodialysis we collected samples on their non-dialysis days to lower the potential acute impact on dialysis procedure on biomarker levels. For control participants (without CKD), we collected blood samples at baseline only. After collection, whole blood was allowed to clot for 20 min at room temperature. We then centrifuged the sample at 1500 × *g* for 10 min at 4°C. The resultant supernatant was collected and stored at −80°C.

We measured serum NfL, pTau181, GFAP, Aβ42, and Aβ40 using a Simoa HD-X (Quanterix, Billerica, MA). Kits were run for pTau181 (v2.1) and neuro 4 plex E (N4PE) according to manufacturer instructions with appropriate standards and quality control samples.[19] Quality controls (QC's) were run at the beginning and end of each plate. All QCs were within range and quality control coefficients of variation for all analytes across runs were below 6%. Specifically, coefficients of variation for serum NfL, pTau181, GFAP, Aβ42, and Aβ40 across plates were 3.30%, 4.95%, 3.88%, 1.99%, and 2.04%, respectively. All samples and QC's were run in duplicate, and the mean concentration of the blood biomarkers was recorded from each blood sample. Additionally, the ratio of Aβ42 to Aβ40 was calculated for each sample (Aβ42/40).

2.5 | Cognitive function assessment

Trained psychometricians or research personnel, certified by trained psychometricians, administered the neuropsychological tests in a private space designated for cognitive testing. The neuropsychological examination included tests from the Uniform Data Set (UDS) version 2.0 used by the national ADRC network.[20]

We used unadjusted z-scores and computed a "global cognition" score by averaging the normed scores from all individual tests in the UDS 2.0 test battery.[21] Additionally, "domain" scores were computed by averaging scores from the UDS tests falling within specific cognitive domains, including Dementia Severity (Mini-Mental State Examination [MMSE]), Memory (Logical Memory, Immediate and Delayed Recall), Language (Animal and Vegetable Verbal Fluency), Attention (Digit Span Forward and Digit Span Backward), Executive Function (Trail Making Test B), and Processing Speed (Trail Making Test A and WAIS Digit Symbol).[21] A composite global cognition z-score was compiled for 44 CKD patients (two of the CKD patients did not undergo cognitive function assessment) at pre-transplant, 12-week, and 12-month post-transplant visits, along with 13 control participants.

RESEARCH IN CONTEXT

1. **Systematic review**: Our literature review, utilizing traditional sources (e.g., PubMed), on Alzheimer's disease (AD) blood biomarkers in chronic kidney disease (CKD), revealed a research gap regarding the AD biomarkers in kidney transplantation. While these biomarkers have potential in AD diagnosis, they may not be as reliable in CKD.
2. **Interpretation**: Our findings show that AD biomarker levels are high in CKD and decrease dramatically with improvement in kidney function with kidney transplantation. Thus, the elevation in AD biomarkers in CKD may be due to decreased renal elimination of these biomarkers.
3. **Future directions**: While our results establish that AD biomarkers are elevated in CKD and decrease after kidney transplantation, the pathological significance of these biomarkers in CKD and their direct contribution to cognitive impairment remain uncertain. Future studies should clarify the significance of these biomarkers for CKD-related cognitive changes, aiming to enhance diagnostic and treatment approaches in AD.

2.6 | Kidney function assessment

Serum creatinine was recorded for each visit from the medical records since it is common for transplant recipients to have frequent laboratory assessment. The laboratory value that was closest to the study visit and within 3 months of the visit was used. The eGFR was calculated using the modification of diet in renal disease study equation using this serum creatinine value.[22]

2.7 | Statistical analyses

Descriptive statistics were used to describe baseline characteristics. Linear mixed models were used to assess the associations between serum biomarker levels and participant group (pre-transplant, post-transplant, and control). Given established relationships between these serum biomarkers and age, we used age for covariate adjustment in all analyses. A further assessment was also conducted to assess whether body mass index (BMI) influenced these results. Linear mixed models with a random intercept accommodated for the repeated measures among patients with CKD, each of whom contributed one to three measures at different timepoints. Spaghetti plots with average age-adjusted group means were produced using these models. Model residuals and normal Q-Q plots were analyzed for

each model to determine model fit and validate model assumptions of normality. Linear contrasts were estimated and were compared to t-distributions to assess for differences between groups (pre-transplant, post-transplant, and control). All statistical analyses were performed using SAS version 9.4.

A similar methodology was used to model the relationship between kidney function (measured by eGFR) and biomarker levels, except that eGFR was used as the primary explanatory variable in place of group. Pre-transplant eGFR and biomarker levels of patients who were on dialysis before kidney transplant were excluded from these models, though post-transplant eGFR and biomarker levels were used if available regardless of a patient's pre-transplant dialysis status. Similar plots and regression analyses were conducted for these models. For models violating assumptions, log transformations were applied.

For analyzing cognitive function, we used a similar approach to the ones described above, using the composite global cognition score as the response variable and biomarker level as the primary explanatory variable. The purpose of producing these models was to verify the relationship between cognition and biomarker levels. Similar plots and regression analyses were conducted for these models.

3 | RESULTS

3.1 | Participant characteristics

The demographic and clinical characteristics of the 46 patients with CKD are detailed in Table 1. The mean age of the cohort was 51.9 ± 12.1 years, with 41% females, and 85% White individuals. Most participants had some level of college education. Comorbid conditions such as hypertension and diabetes were common among the cohort. The common causes for kidney failure included diabetes, hypertension, and autosomal dominant polycystic kidney disease. Notably, 10 participants (22%) were not on chronic dialysis at the time of their pre-transplant visit. All 46 patients underwent a kidney transplant within 1 year of the pre-transplant visit. Some patients missed the post-transplant visits during the COVID-19 pandemic; 35 completed the 12-week post-transplant biomarker assessments while 31 completed the 12-month post-transplant biomarker assessments, as shown in Figure S1. All patients received immunosuppression per institutional protocol; thymoglobulin or basiliximab and steroids for induction and an anti-metabolite and calcineurin inhibitor for maintenance.

There were 13 participants in the control group without CKD. Control participants were of similar age to the CKD group (50.7 ± 7.5 years old), with 54% females, and 85% White individuals. All control participants had received at least some college education.

TABLE 1 Demographic and clinical characteristics of study participants with chronic kidney disease ($n = 46$).

Patient characteristics	
Female sex, *n* (%)	19 (41)
Age (years), mean ± SD	51.9 ± 12.10
Race, *n* (%)	
White	39 (85)
Black or African American	6 (13)
Other	1 (2)
Ethnicity, *n* (%)	
Hispanic or Latino	1 (2)
Not Hispanic or Latino	45 (98)
Body mass index (BMI) (kg/m^2), mean ± SD	30.1 ± 5.32
Education level[a], *n* (%)	
High school diploma, no college	8 (18)
Some college	18 (40)
Has 4-year degree	8 (18)
Attended graduate school	11 (24)
Comorbid conditions[b], *n* (%)	
Coronary artery disease	6 (13)
Diabetes	11 (24)
Hypertension	41 (89)
Depression	12 (26)
Smoking	11 (24)
Dialysis modality, *n* (%)	
In-home hemodialysis	3 (7)
In-center hemodialysis	20 (43)
Peritoneal dialysis	13 (28)
No dialysis prior to KT	10 (22)
Causes of kidney failure, *n* (%)	
Diabetes	9 (20)
Hypertension	10 (22)
ADPKD	9 (20)
Glomerulonephritis	3 (7)
Unknown	1 (2)
Other	25 (54)

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; KT, kidney transplant.

[a]Education level was missing in one participant.

[b]History of coronary artery disease was defined as a history of myocardial infarction, coronary angioplasty, or coronary artery bypass grafting. Diabetes was defined as past or current use of oral hypoglycemics or insulin. Hypertension was defined as past or current use of antihypertensives. Depression was defined as use of anti-depressants or self-report of feeling depressed. Smoking was defined as use of cigarettes in the past 100 days.

3.2 | AD blood biomarker levels before and after kidney transplantation

The unadjusted mean levels of AD blood biomarkers in control participants and CKD patients at various stages of transplantation are shown in Table 2. The levels of all individual biomarkers studied were higher in CKD patients when compared to controls. Pre-transplant NfL levels (117 ± 71.6 pg/mL), were more than 10 times higher than the levels in the controls (11.3 ± 4.60 pg/mL). Similarly, other biomarkers

TABLE 2 Alzheimer's disease blood biomarker levels before and after kidney transplantation.

Group	NfL	pTau181	GFAP	Aβ42	Aβ40	Aβ42/40
Control	11.31 ± 4.60	13.14 ± 7.74	94.0 ± 38.9	5.34 ± 1.42	72.0 ± 16.72	0.074 ± 0.009
Pre-KT	116.92 ± 71.61	74.91 ± 42.41	193.25 ± 127.30	17.02 ± 4.99	258.57 ± 95.89	0.069 ± 0.015
12 weeks post-KT	27.69 ± 13.51	21.60 ± 8.66	132.61 ± 83.29	7.42 ± 2.39	102.93 ± 28.66	0.072 ± 0.013
12 months post-KT	26.0 ± 12.44	21.89 ± 10.49	112.42 ± 42.60	6.27 ± 2.06	89.87 ± 24.73	0.070 ± 0.014

Note: Biomarker values are reported as mean ± SD and in pg/mL.
Abbreviations: Aβ40, amyloid β 40; Aβ42, amyloid β 42; Aβ42/40, amyloid β 42/40.; GFAP, glial fibrillary acidic protein; KT, kidney transplant; NfL, neurofilament light; pTau181, phosphorylated tau 181.

TABLE 3 Mixed model analysis of Alzheimer's disease blood biomarker levels before and after kidney transplantation.

Comparison	Biomarker	β (SE)[a]	*p*-Value
Control versus pre-transplant	NfL	-103.3 (14.92)	< 0.0001
	pTau181	-61.38 (8.78)	< 0.0001
	GFAP	-94.87 (28.48)	0.002
	Aβ42	-11.64 (1.14)	< 0.0001
	Aβ40	-184.38 (19.35)	< 0.0001
	Aβ42/Aβ40	0.005 (0.004)	0.23
Pre-transplant versus post-transplant	NfL	87.89 (6.46)	< 0.0001
	pTau181	49.07 (4.26)	< 0.0001
	GFAP	62.33 (9.86)	< 0.0001
	Aβ42	10.25 (0.641)	< 0.0001
	Aβ40	161.76 (12.41)	< 0.0001
	Aβ42/Aβ40	-0.004 (0.002)	0.03
Control versus post-transplant	NfL	-15.44 (15.09)	0.31
	pTau181	-12.32 (8.69)	0.16
	GFAP	-32.54 (28.76)	0.26
	Aβ42	-1.39 (1.15)	0.23
	Aβ40	-22.63 (19.07)	0.24
	Aβ42/Aβ40	0.0008 (0.004)	0.84

Abbreviations: Aβ40, amyloid β 40; Aβ42, amyloid β 42; Aβ42/40, amyloid β 42/40.; GFAP, glial fibrillary acidic protein; NfL, neurofilament light; pTau181, phosphorylated tau 181.
[a]β represents estimated difference of first group minus second group adjusted for age. For example, control minus pre-transplant for control versus pre-transplant.

were also higher in CKD when compared to the controls; pTau181 was 74.9 ± 42.4 pg/mL in CKD (vs. 13.1 ± 7.74 pg/mL in controls), GFAP was 193 ± 127 pg/mL (vs. 94.0 ± 38.9 pg/mL in controls), Aβ42 was 17.0 ± 4.99 pg/mL (vs. 5.34 ± 1.42 pg/mL in controls), and Aβ40 was 259 ± 95.9 pg/mL (vs. 72.0 ± 16.7 pg/mL in controls).

After adjusting for age, the differences observed in biomarker levels persisted, as indicated by the linear mixed model analysis presented in Table 3. The analysis revealed high levels of all individual biomarkers in CKD patients compared to controls, and no difference in the Aβ42/40 ratio between the two groups. Including BMI as a covariate to these models resulted in *p* value > 0.28 for all estimated BMI coefficients except for the model for GFAP that had *p* value = 0.06. However, inferential conclusions with respect to our parameters of interest described above were not altered.

Following kidney transplantation, the biomarker levels decreased dramatically as shown in Table 2 (unadjusted), Table 3 (adjusted), and Figure 1. NfL levels decreased by more than 76% at 12 weeks post-transplant, along with significant decreases in pTau181, GFAP, Aβ42, and Aβ40 by 71%, 31%, 56%, and 60%, respectively. Despite the decrease in the biomarker levels after kidney transplantation, individual biomarker levels remained slightly higher than controls, but this difference was not statistically significant (*p* value > 0.05 for all linear contrast comparisons). Additionally, separating the pre-transplant group by dialysis status did not affect the results (Table S1).

There were no changes in the levels of NfL, pTau181, and GFAP from 12 weeks to 12 months post-transplant (Table 2). However, there was a decrease in levels of Aβ42 (mean change = 1.10 ± 1.50, *p* value = 0.002), Aβ40 (11.57 ± 20.92, *p* value = 0.01), and the Aβ42/40 ratio (0.003 ± 0.007, *p* value = 0.05) from the 12-week to 12-month post-transplant visits.

Overall, all individual biomarker values were high in CKD compared to control participants and normalized (decreased) with kidney transplantation. The Aβ42/40 ratio increased (improved) in CKD patients from pre-transplant to post-transplant.

3.3 | AD biomarker levels and kidney function

Prior to kidney transplant, patients with CKD were either on dialysis or had very low eGFRs. Pre-transplant eGFR of patients not on dialysis was 7.90 ± 3.87 mL/min/1.73 m^2. In comparison, the mean eGFR for control participants was 92.4 ± 16.0 mL/min/1.73 m^2. Although there was an improvement in eGFR after transplantation the eGFR remained lower than that of control participants. The mean eGFR at 12 weeks post-transplant was 49.1 ± 13.6 mL/min/1.73 m^2 and at 12 months post-transplant was 51.5 ± 15.3 mL/min/1.73 m^2.

Patients with CKD who were on dialysis pre-transplant (and hence with minimal kidney function) had significantly higher levels of several blood biomarkers compared to those who were not on dialysis, as shown in Table 4. The mean difference between the two groups was 70.8 ± 72.2 pg/mL (*p* value = 0.01) for NfL, 36.3 ± 16.1 pg/mL (*p* value = 0.03) for pTau181, 5.11 ± 5.09 pg/mL (*p* value = 0.01) for Aβ42, and 78.8 ± 91.1 pg/mL (*p* value = 0.02) for Aβ40 compared to patients with CKD who were not on dialysis. In contrast, GFAP and the Aβ42/40

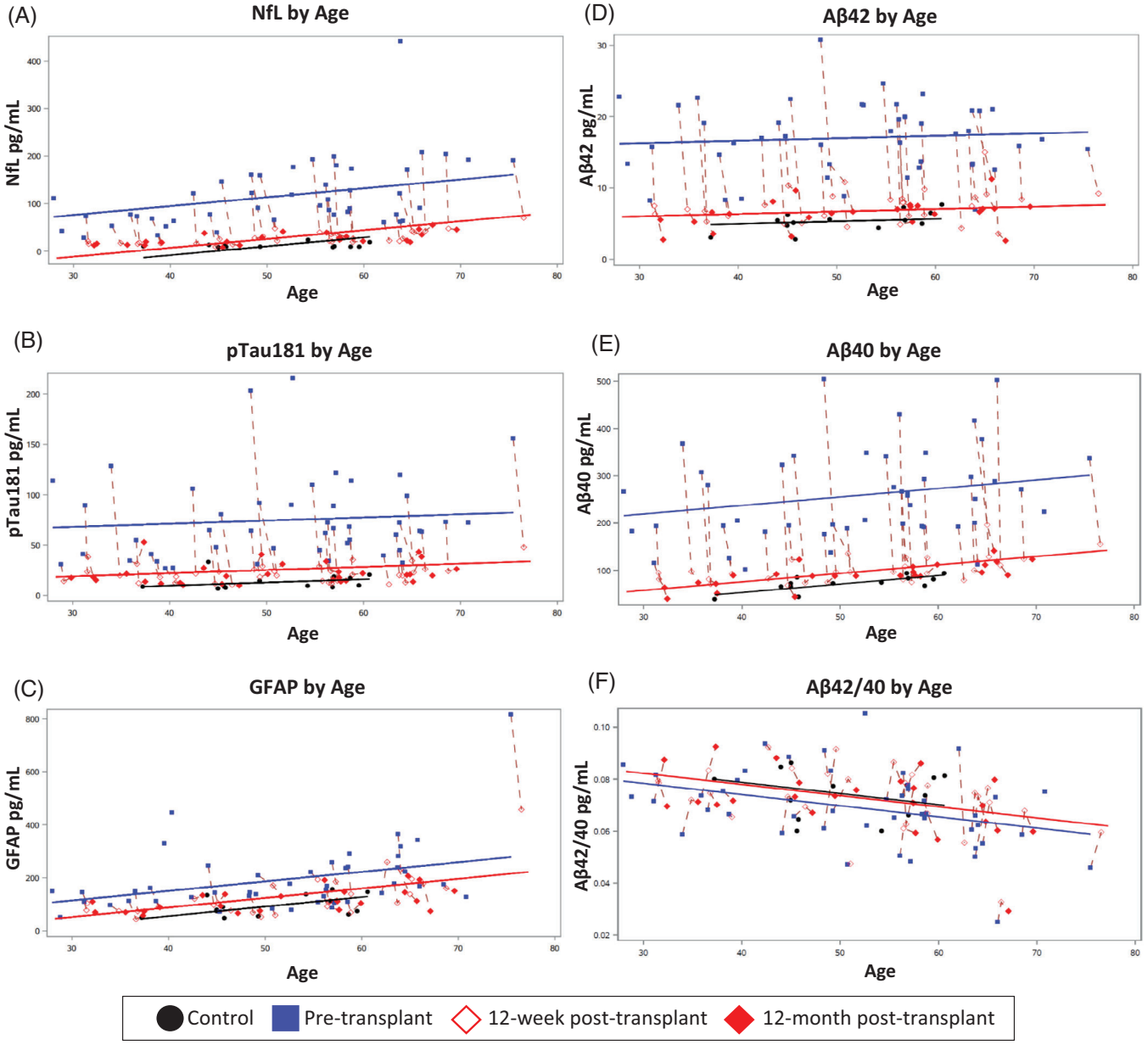

FIGURE 1 Alzheimer's disease blood biomarker levels (A) neurofilament light (NfL), (B) phosphorylated tau 181 (pTau181), (C) glial fibrillary acidic protein (GFAP), (D) amyloid β 42 (Aβ42), (E) amyloid β 40 (Aβ40), and (F) amyloid β 42/40 (Aβ42/40) by age. Scatterplots display individual participant data as a function of age and group (pre-transplant: blue squares; 12 weeks post-transplant: red empty diamonds; 12 months post-transplant: red solid diamonds; controls: black circles). Dashed lines represent individual participant trajectory over time. The distance between the solid lines (blue for pre-transplant, red for post-transplant, and black for controls) represents the estimated group main effect (i.e., intercept) differences. The slope of the solid lines represents the overall effect of age

ratio did not show significant differences based on dialysis status, with *p*-values of 0.89 for both biomarkers.

Table S2 shows the association between the eGFR and biomarker levels. Figure S2 shows the trajectory of the biomarker levels and eGFR before and after transplantation. Individual blood biomarker levels decreased with an improvement in eGFR. The Aβ42/40 ratio did not differ by eGFR values. The biomarker levels in the control participants were lower (and their eGFR higher) than the CKD patients.

3.4 | AD blood biomarkers and cognitive function

Table S3 presents the compositive global cognition z-scores at different time points for CKD patients and for controls. Performance on the cognitive test battery improved following kidney transplantation. The improvement in global cognitive function aligned with the decrease in individual blood biomarkers tested (Figure S3). The linear mixed-effects model analysis revealed robust associations between cognitive

TABLE 4 Alzheimer's disease blood biomarker levels based on dialysis status.

	Dialysis status		Difference
Fluid biomarker	Yes ($n = 36$)	No ($n = 10$)	Yes—No (p-value)
NfL	128.8 ± 79.25	58.05 ± 28.97	70.78 ± 72.2 (0.01)
pTau181	79.89 ± 46.93	43.61 ± 17.96	36.27 ± 16.1 (0.03)
GFAP	185.6 ± 139.1	192.4 ± 111.7	-6.80 ± 134 (0.89)
Aβ42	17.52 ± 5.17	12.41 ± 4.76	5.11 ± 5.09 (0.01)
Aβ40	275.7 ± 98.36	196.9 ± 54.25	78.81 ± 91.1 (0.02)
Aβ42/40	0.07 ± 0.02	0.07 ± 0.01	-0.0007 ± 0.02 (0.89)

Note: Results indicate pre-transplant biomarker values as mean ± SD. Difference yes-no indicates pooled difference between the biomarker values in patients on dialysis and those not on dialysis at the pre-transplant visit.
Abbreviations: Aβ40, amyloid β 40; Aβ42, amyloid β 42; Aβ42/40, amyloid β 42/40.; GFAP, glial fibrillary acidic protein; NfL, neurofilament light; pTau181, phosphorylated tau 181.

TABLE 5 Alzheimer's disease blood biomarker levels and cognitive function.

Biomarker	β (SE)	p-Value
NfL	-0.003 (0.0006)	< 0.0001
pTau181	-0.006 (0.001)	< 0.0001
GFAP	-0.002 (0.0006)	0.005
Aβ42	-0.037 (0.005)	< 0.0001
Aβ40	-0.002 (0.0003)	< 0.0001
Aβ42/Aβ40	2.43 (4.71)	0.61

Note: Analysis includes participants with cognitive assessment in addition to biomarker values ($n = 57$, 44 CKD participants, and 13 control participants). β represents estimated coefficients of linear relationship of biomarkers with cognitive z-score from linear mixed models adjusted for age.
Abbreviations: Aβ40, amyloid β 40; Aβ42, amyloid β 42; Aβ42/40, amyloid β 42/40.; GFAP, glial fibrillary acidic protein; NfL, neurofilament light; pTau181, phosphorylated tau 181.

function and individual blood biomarkers after adjusting for age, as shown in Table 5.

4 | DISCUSSION

In this study, we showed that patients with CKD have remarkably elevated levels of AD blood biomarkers. Notably, NfL was > 10-fold higher in CKD than in controls without CKD and more than double the levels seen in individuals with AD.[23] Furthermore, we identified that patients on dialysis had higher biomarker levels compared to those not on dialysis. Following kidney transplantation, there was a dramatic change in AD biomarker levels. This improvement in biomarker levels coincided with enhancements in cognitive function after kidney transplantation. These findings introduce a novel clinical perspective in use of these biomarkers in CKD.

Biomarker levels decreased strikingly following a kidney transplant but remained slightly elevated compared to control participants. Kidney transplantation is an event with large changes in eGFR. Despite this, the kidney function in transplant recipients is not perfect. Kidney transplant recipients have a single functioning kidney as opposed to individuals without CKD who have two functional kidneys. Thus, even with a seemingly normal serum creatinine level, transplant recipients have less than half the number of functional nephrons when compared to individuals without CKD. It is also possible that the transplanted kidney is from a donor with mild CKD or undergoes damage during the peri-transplant period during organ retrieval, transportation, or transplantation, further decreasing the kidney function. The small difference in post-transplant biomarker levels when compared to the controls may indicate lower kidney function in the post-transplant group. Since the post-transplant biomarker levels were not detected to be significantly different compared to controls, this may also indicate that mildly low eGFR may not have a large effect on AD biomarker levels.

Consistent with other reports,[24,25] cognitive function also improved with kidney transplantation. The improvement in cognitive function tracked with improvement in AD biomarker levels. NfL is a biomarker for axonal injury[23] and GFAP represents astroglia activation[26] and gliosis which are likely to improve with kidney transplantation. Previous reports have suggested that NfL levels are associated with fractional anisotropy (FA) and mean diffusivity (MD) measured by diffusion tensor imaging.[27] We have previously shown that both FA and MD change with kidney transplantation.[28,29] The decrease in NfL levels after transplantation may reflect improvement in white matter damage observed in CKD.

While the individual AD biomarker levels were affected by eGFR, the Aβ42/40 ratio was not. This is similar to the findings by Zhang et al.[30] and indicates that the elevation in AD biomarkers may be due to differences in elimination of these biomarkers by the kidneys. Glomerular filtration is dependent on several factors including their metabolism, water solubility, polarity or charge, size, and protein binding. The AD biomarkers are generally at the mid to upper limit of the size that can be easily filtered through the glomerular filtration barrier. In addition, tubular section also plays a role in the elimination of substances.[31] While individual biomarkers may be affected by kidney function, the ratio of Aβ42 and Aβ40 may eliminate the effect of reduced eGFR or tubular secretion. Previous studies have indicated

higher AD biomarker levels in CKD without clear association with cerebral amyloid deposition.[30,32] Thus, elevated AD biomarker levels in CKD may be due to lower elimination of these biomarkers by the kidneys rather than improvement in cerebral amyloid pathology. Although we did not evaluate cerebral amyloid in this study, it is hard to imagine a near complete resolution of amyloid deposits in a 12-week period. Further, we did not see changes in AD biomarker levels between 12 weeks and 12 months post-transplant suggesting continued resorption of cerebral amyloid.

The study's strength lies in its prospective longitudinal design, tracking changes in biomarkers alongside cognitive function before and after kidney transplantation. We adjusted our analysis for age as levels of these AD biomarkers generally increase with age. We also assessed biomarkers, kidney function, and cognition in controls of a similar age without CKD or dementia for comparison. Although we have a smaller number of controls, the age range for controls is within the age range of CKD patients. The small sample size, lack of assessment of amyloid burden using neuroimaging, use of non-ethylenediamine tetraacetic acid (EDTA) plasma samples, and limited generalizability being a single center study are limitations of the study. Despite the small size, the unique group of patients undergoing transplantation with a rapid improvement in eGFR, and a longitudinal follow up offers valuable data.

The data from this study are clinically relevant. The prevalence of both CKD and AD increases with age. Identification of patients with CKD and the consideration that AD biomarkers may be elevated due to CKD is clinically important. CKD is an independent risk factor for dementia and up to 50% of patients with mild to moderate CKD have cognitive impairment.[33–38] In fact, the risk of mild cognitive impairment and dementia with CKD is ahead of genetic factors and is only exceeded by stroke and chronic use of anxiolytics. The mechanisms underlying cognitive impairment in CKD may however differ from those in AD. Autopsy and amyloid PET studies indicate that despite higher prevalence of cognitive impairment, patients with CKD do not have a higher prevalence of typical cerebral amyloid and tau pathology seen in AD.[10,39,40] CKD is however associated with cerebral amyloid angiopathy[40] which in theory could contribute to elevated Aβ levels in CKD. While it is common for patients with CKD to get diagnosed with AD, this diagnosis is generally made clinically without confirmation of the presence of cerebral amyloid plaques.[41] It is possible that factors other than amyloid, such as white matter disease, lacunar strokes, microbleeds, and metabolic effects of uremic toxins may play a more important role in cognitive impairment in CKD.[28] With these differences in the pathophysiology of AD and cognitive impairment in CKD and considering the availability of new anti-amyloid antibody treatment options for AD, it is important to identify CKD patients with and without AD. AD blood biomarkers may be limited in their ability to make this distinction. These assessments are further complicated by the fact that eGFR is often derived from serum creatinine, which is based on muscle mass. As an individual develops sarcopenia (which is associated with dementia), their eGFR can appear normal despite significant CKD. Thus, these data advocate for enhanced monitoring and oversight while interpreting biomarker levels in individuals with CKD. These data prompt considerations for future research directions. The investigation of cognitive impairment in CKD and identification of 'normal' ranges of biomarkers in CKD represent crucial next steps.

In conclusion, AD blood biomarkers are elevated in CKD and decrease with improvement in kidney function following kidney transplant. Cognitive function also improves with transplantation and tracks the changes in AD biomarkers.

ACKNOWLEDGMENTS

This work was supported by National Institutes of Health (NIH) grant K23 AG055666 (to A.G.), Kidney Institute Pilot grant (to A.G.), R01AG062548 and R01AG081304 (to JKM), NIH grants P30 AG035982 (to the University of Kansas Alzheimer's Disease Research Center), and UL1TR002366 (to the University of Kansas for Frontiers CTSA).

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest relevant to this manuscript. Author disclosures are available in the supporting information.

CONSENT STATEMENT

All subjects involved in this study provided informed consent prior to their participation. The consent process was conducted in accordance with ethical standards, and participants were informed about the nature of the study, its purpose, and any potential risks involved. Confidentiality and anonymity were assured to all participants.

ORCID


Aditi Gupta https://orcid.org/0000-0002-6286-802X

REFERENCES

1. Organization WH. Global status report on the public health response to dementia. 2021.
2. Planche V, Bouteloup V, Pellegrin I, et al. Validity and performance of blood biomarkers for Alzheimer disease to predict dementia risk in a large clinic-based cohort. *Neurology*. 2023;100(5):e473-e484.
3. Ossenkoppele R, van der Kant R, Hansson O. Tau biomarkers in Alzheimer's disease: towards implementation in clinical practice and trials. *Lancet Neurol*. 2022;21(8):726-734.
4. Huang X, Yuan S, Ling Y, et al. Evaluating the effect of kidney function on brain volumes and dementia risk in the UK Biobank. *Arch Gerontol Geriatr*. 2024;116:105157.
5. Kurella Tamura M, Gaussoin SA, Pajewski NM, et al. Kidney disease, intensive hypertension treatment, and risk for dementia and mild cognitive impairment: the systolic blood pressure intervention trial. *J Am Soc Nephrol*. 2020;31(9):2122-2132.
6. Janelidze S, Barthelemy NR, He Y, Bateman RJ, Hansson O. Mitigating the associations of kidney dysfunction with blood biomarkers of Alzheimer disease by using phosphorylated tau to total tau ratios. *JAMA Neurol*. 2023;80(5):516-522.
7. Lehmann S, Schraen-Maschke S, Vidal JS, et al. Plasma phosphorylated tau 181 predicts amyloid status and conversion to dementia stage dependent on renal function. *J Neurol Neurosurg Psychiatry*. 2023;94(6):411-419.
8. Ramanan VK, Graff-Radford J, Syrjanen J, et al. Association of plasma biomarkers of Alzheimer disease with cognition and medical comorbidities in a biracial cohort. *Neurology*. 2023;101(14):e1402-e1411.

9. Syrjanen JA, Campbell MR, Algeciras-Schimnich A, et al. Associations of amyloid and neurodegeneration plasma biomarkers with comorbidities. *Alzheimers Dement*. 2022;18(6):1128-1140.
10. Stocker H, Beyer L, Trares K, et al. Association of kidney function with development of Alzheimer disease and other dementias and dementia-related blood biomarkers. *JAMA Netw Open*. 2023;6(1):e2252387.
11. Pichet Binette A, Janelidze S, Cullen N, et al. Confounding factors of Alzheimer's disease plasma biomarkers and their impact on clinical performance. *Alzheimers Dement*. 2023;19(4):1403-1414.
12. Mielke MM, Dage JL, Frank RD, et al. Performance of plasma phosphorylated tau 181 and 217 in the community. *Nat Med*. 2022;28(7):1398-1405.
13. Zakiyanov O, Kalousová M, Zima T, Tesař V. Placental growth factor in patients with decreased renal function. *Ren Fail*. 2011;33(3):291-297.
14. Dittrich A, Ashton NJ, Zetterberg H, et al. Association of chronic kidney disease with plasma NfL and other biomarkers of neurodegeneration: the H70 Birth Cohort Study in Gothenburg. *Neurology*. 2023;101(3):e277-e288.
15. Gronewold J, Todica O, Klafki HW, et al. Association of plasma β-amyloid with cognitive performance and decline in chronic kidney disease. *Mol Neurobiol*. 2017;54(9):7194-7203.
16. Tian DY, Cheng Y, Zhuang ZQ, et al. Physiological clearance of amyloid-beta by the kidney and its therapeutic potential for Alzheimer's disease. *Mol Psychiatry*. 2021;26(10):6074-6082.
17. Verde F, Milone I, Dubini A, et al. Influence of kidney function and CSF/serum albumin ratio on plasma Abeta42 and Abeta40 levels measured on a fully automated platform in patients with Alzheimer's disease. *Neurol Sci*. 2023;44(9):3287-3290.
18. Kovesdy CP. Epidemiology of chronic kidney disease: an update 2022. *Kidney Int Suppl (2011)*. 2022;12(1):7-11.
19. Green ZD, Kueck PJ, John CS, Burns JM, Morris JK. Blood biomarkers discriminate cerebral amyloid status and cognitive diagnosis when collected with ACD-A anticoagulant. *Curr Alzheimer Res*. 2023;20(8):557-566.
20. Morris JC, Weintraub S, Chui HC, et al. The Uniform Data Set (UDS): clinical and cognitive variables and descriptive data from Alzheimer disease centers. *Alzheimer Dis Assoc Disord*. 2006;20(4):210-216.
21. Shirk SD, Mitchell MB, Shaughnessy LW, et al. A web-based normative calculator for the uniform data set (UDS) neuropsychological test battery. *Alzheimers Res Ther*. 2011;3(6):32.
22. Levey AS, Coresh J, Greene T, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med*. 2006;145(4):247-254.
23. Mattsson N, Cullen NC, Andreasson U, Zetterberg H, Blennow K. Association between longitudinal plasma neurofilament light and neurodegeneration in patients with Alzheimer disease. *JAMA Neurol*. 2019;76(7):791-799.
24. Gupta A, Mahnken JD, Bernal J, et al. Changes in cognitive function after kidney transplantation: a longitudinal cohort study. *Am J Kidney Dis*. 2024.
25. Jurgensen A, Qannus AA, Gupta A. Cognitive function in kidney transplantation. *Curr Transplant Rep*. 2020;7:145-153.
26. Elahi FM, Casaletto KB, La Joie R, et al. Plasma biomarkers of astrocytic and neuronal dysfunction in early- and late-onset Alzheimer's disease. *Alzheimers Dement*. 2020;16(4):681-695.
27. Beydoun MA, Noren Hooten N, Weiss J, et al. Plasma neurofilament light as blood marker for poor brain white matter integrity among middle-aged urban adults. *Neurobiol Aging*. 2023;121:52-63.
28. Lepping RJ, Montgomery RN, Sharma P, et al. Normalization of cerebral blood flow, neurochemicals, and white matter integrity after kidney transplantation. *J Am Soc Nephrol*. 2021;32(1):177.
29. Gupta A, Lepping RJ, Yu AS, et al. Cognitive function and white matter changes associated with renal transplantation. *Am J Nephrol*. 2016;43(1):50-57.
30. Zhang B, Zhang C, Wang Y, et al. Effect of renal function on the diagnostic performance of plasma biomarkers for Alzheimer's disease. *Front Aging Neurosci*. 2023;15:1150510.
31. Suchy-Dicey AM, Laha T, Hoofnagle A, et al. Tubular Secretion in CKD. *J Am Soc Nephrol*. 2016;27(7):2148-2155.
32. Sedaghat S, Ji Y, Hughes TM, et al. The association of kidney function with plasma amyloid-β levels and brain amyloid deposition. *J Alzheimers Dis*. 2023;92(1):229-239.
33. Lipnicki DM, Crawford J, Kochan NA, et al. Risk factors for mild cognitive impairment, dementia and mortality: the sydney memory and ageing study. *J Am Med Dir Assoc*. 2017;18(5):388-395.
34. Xu H, Garcia-Ptacek S, Trevisan M, et al. Kidney function, kidney function decline, and the risk of dementia in older adults: a registry-based study. *Neurology*. 2021;96(24):e2956-e2965.
35. Wang M, Ding D, Zhao Q, et al. Kidney function and dementia risk in community-dwelling older adults: the Shanghai Aging Study. *Alzheimer's Research & Therapy*. 2021;13(1):21.
36. Yaffe K, Ackerson L, Kurella Tamura M, et al. Chronic kidney disease and cognitive function in older adults: findings from the chronic renal insufficiency cohort cognitive study. *J Am Geriatr Soc*. 2010;58(2):338-345.
37. Richardson C, Nilforooshan R, Gard PR, Weaving G, Tabet N. Impaired renal function and biomarkers of vascular disease in Alzheimer's disease. *Current Alzheimer Research*. 2014;11(3):253-258.
38. Kerr E, Craig D, McGuinness B, et al. Reduced estimated glomerular filtration rate in Alzheimer's disease. *Int J Geriatr Psychiatry*. 2009;24(9):927-932.
39. Lau WL, Fisher M, Fletcher E, et al. Kidney function is not related to brain amyloid burden on PET imaging in The 90+ Study Cohort. *Front Med (Lausanne)*. 2021;8:671945.
40. Wang S, Wang J, Dove A, et al. Association of impaired kidney function with dementia and brain pathologies: a community-based cohort study. *Alzheimers Dement*. 2023;19(7):2765-2773.
41. McAdams-DeMarco MA, Daubresse M, Bae S, Gross AL, Carlson MC, Segev DL. Dementia, Alzheimer's disease, and mortality after hemodialysis initiation. *Clinical J Am Soc Nephrol: CJASN*. 2018;13(9):1339-1347.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Blankenship AE, Yoksh L, Kueck PJ, Mahnken JD, Morris JK, Gupta A. Changes in Alzheimer's disease blood biomarkers in kidney failure before and after kidney transplant. *Alzheimer's Dement*. 2024;:e12614. https://doi.org/10.1002/dad2.12614