Molecular Neurobiology (2023) 60:5343–5351
https://doi.org/10.1007/s12035-023-03420-w

ORIGINAL ARTICLE

Associations of Blood and Cerebrospinal Fluid Aβ and tau Levels with Renal Function

Hao-Lun Sun[1,2] · Xiu-Qing Yao[7] · Li Lei[1,3] · Wang-Sheng Jin[1,3] · Yu-Di Bai[1,3] · Gui-Hua Zeng[1,3] · An-Yu Shi[1,3] · Jun Liang[2] · Li Zhu[2] · Yu-Hui Liu[1,3,4,5] · Yan-Jiang Wang[1,3,4,5,6] · Xian-Le Bu[1,3,4,5]

Received: 26 January 2023 / Accepted: 25 May 2023 / Published online: 13 June 2023

Abstract

Amyloid β (Aβ) and tau play pivotal roles in the pathogenesis of Alzheimer's disease (AD). Previous studies have shown that brain-derived Aβ and tau can be cleared through transport into the periphery, and the kidneys may be vital organs involved in the clearance of Aβ and tau. However, the effects of deficiency in the clearance of Aβ and tau by the kidneys on brain AD-type pathologies in humans remain largely unknown. In this study, we first recruited 41 patients with chronic kidney disease (CKD) and 40 age- and sex-matched controls with normal renal function to analyze the associations of the estimated glomerular filtration rate (eGFR) with plasma Aβ and tau levels. To analyze the associations of eGFR with cerebrospinal fluid (CSF) AD biomarkers, we recruited 42 cognitively normal CKD patients and 150 cognitively normal controls with CSF samples. Compared with controls with normal renal function, CKD patients had higher plasma levels of Aβ40, Aβ42 and total tau (T-tau), lower CSF levels of Aβ40 and Aβ42 and higher levels of CSF T-tau/Aβ42 and phosphorylated tau (P-tau)/Aβ42. Plasma Aβ40, Aβ42, and T-tau levels were negatively correlated with eGFR. In addition, eGFR was negatively correlated with CSF levels of T-tau, T-tau/Aβ42, and P-tau/Aβ42 but positively correlated with Mini-Mental State Examination (MMSE) scores. Thus, this study showed that the decline in renal function was correlated with abnormal AD biomarkers and cognitive decline, which provides human evidence that renal function may be involved in the pathogenesis of AD.

Keywords Alzheimer's disease · Renal function · β-amyloid · Tau · Cognitive function

Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disease causing cognitive decline among elderly individuals [1]. Extracellular neuritic plaques consisting of β-amyloid (Aβ) and intracellular neurofibrillary tangles formed by phosphorylated tau are the two most characteristic pathological hallmarks of AD [2]. Pathological proteins can efflux into the periphery via the blood–brain barrier (BBB) and glymphatic system [3]. The peripheral system shows physiological abilities of scavenging Aβ and tau [4, 5]. A growing number of studies suggests that abnormal

Hao-Lun Sun and Xiu-Qing Yao contributed equally to this work.

✉ Yan-Jiang Wang
yanjiang_wang@tmmu.edu.cn

✉ Xian-Le Bu
buxianle@sina.cn

1 Department of Neurology and Centre for Clinical Neuroscience, Daping Hospital, Third Military Medical University, Chongqing, China

2 Shigatse Branch, Xinqiao Hospital, Third Military Medical University, Shigatse, China

3 Chongqing Key Laboratory of Ageing and Brain Diseases, Chongqing, China

4 Institute of Brain and Intelligence, Third Military Medical University, Chongqing, China

5 State Key Laboratory of Trauma, Burns and Combined Injury, Third Military Medical University, Chongqing, China

6 Center for Excellence in Brain Science and Intelligence Technology, Chinese Academy of Sciences, Shanghai, China

7 Department of Rehabilitation, The Second Affiliated Hospital of Chongqing Medical University, Chongqing, China

metabolism of peripheral Aβ and tau plays a crucial role in AD pathogenesis [6–10]. In vitro and in vivo studies indicate that the kidneys may be vital organs involved in the peripheral clearance of Aβ and tau [5, 11]. Previous studies have shown that a decrease in the estimated glomerular filtration rate (eGFR) is associated with an increase in blood Aβ levels [12, 13]. In addition, patients with chronic kidney disease (CKD) are reported to be more prone to developing cognitive impairment and AD [14, 15]. However, the effects of deficiency in the clearance of blood AD-related proteins by kidney on brain AD-type pathologies in humans remain largely unknown. Therefore, in the present study, we aimed to investigate the associations of eGFR with Aβ and tau levels in blood as well as cerebrospinal fluid (CSF).

Materials and Methods

Study Participants

To analyze the associations of eGFR with plasma Aβ and tau levels, we recruited 41 cognitively normal CKD patients and 40 age- and sex-matched cognitively normal controls with normal renal function from Daping Hospital between January and October 2018. All CKD patients were recently diagnosed and had not initiated any type of dialysis. In addition, 42 cognitively normal patients (≥ 60 y) with CKD and 150 healthy aged controls who had undergone surgical treatment for noninflammatory disorders (e.g., benign prostatic hyperplasia, stress incontinence) were recruited in the same hospital from January 2019 to December 2022. Therefore, we were able to collect CSF samples during lumbar anesthesia before surgery to analyze the associations of eGFR with CSF AD biomarkers.

Subjects in the above three groups were excluded if they met any of the following criteria: (1) abnormal cognition assessed by the Chinese version of the Mini-Mental State Examination (MMSE); (2) a family history of AD or other dementia; (3) severe cardiac, pulmonary, hepatic, or neurological diseases; (4) cancers; and (5) unwillingness to participate in the present study. Written consent was obtained from all participants or their legal representatives. This study was approved by the Institutional Review Board of Daping Hospital.

CKD Diagnosis

The diagnosis of CKD was based on the 2012 clinical practice guideline published by the Kidney Disease: Improving Global Outcomes (KDIGO) organization [16]. In brief, the patients had suffered a continuing abnormality in kidney structure or function for more than 3 months, including eGFR ≤ 60 mL/min/1.73 m^2 or urine albumin-to-creatinine ratio ≥ 30 mg/g. eGFR was calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation based on serum creatinine levels [17]. We collected the demographic characteristics and medical history data of all participants.

CSF and Plasma Sampling and Processing

Fasting blood was collected between 06:00 and 07:00 to avoid potential circadian rhythm effects. The blood samples were centrifuged at 2,000 × g for 10 min within one hour after standing and then stored at − 80 °C until use. CSF was also stored at -80 °C after centrifugation at 2,000 × g for 10 min.

Measurements of Aβ and tau Levels

The plasma Aβ40, Aβ42 and total tau (T-tau) levels were measured by the commercially available single-molecule array (SIMOA) Human Neurology 3-Plex A assay kit (Quanterix, Lexington, Massachusetts) on the automated SIMOA HD-1 analyzer. The CSF levels of Aβ, total tau (T-tau) and phosphorylated tau-181 (P-tau) were determined by human Aβ and tau enzyme-linked immunosorbent assay (ELISA) kits (INNOTEST, Fujirebio, Belgium) according to the manufacturer's protocol.

Statistical Analysis

Data are presented as the mean ± standard deviation (SD) unless otherwise stated. The normality of the data was evaluated by the Kolmogorov–Smirnov test. Then, a two-tailed independent t test was used to compare data with a normal distribution, while nonnormal data were compared using the Mann–Whitney U test. The chi-squared test was used to compare categorical variable data. Correlations of eGFR with AD biomarkers were tested by partial correlation analyses adjusted by age, sex and APOE ε4 genotype, and r represents the partial correlation coefficient. We defined two-sided p values less than 0.05 as statistically significant. The statistical analyses were performed with Statistical Product Service Solutions (SPSS), version 25.0 (SPSS Software, USA).

Results

Increased Plasma Aβ and tau Levels in CKD Patients

First, 41 clinically diagnosed CKD patients and 40 age- and sex-matched cognitively normal controls with normal

Table 1 Characteristics of the participants with plasma samples

Characteristics	CON (n = 40)	CKD (n = 41)	*p* value
Age, mean (SD), y	60.63 (14.17)	62.34 (14.96)	0.653
Female, n (%)	19 (47.50)	20 (48.78)	0.908
Hypertension, n (%)	10 (25.00)	11 (26.83)	0.851
Diabetes, n (%)	5 (12.50)	4 (9.76)	0.694
Dyslipidemia, n (%)	9 (22.50)	10 (24.39)	0.841
eGFR, mean (SD), (mL/min/1.73m^2)	124.1 (19.95)	23.57 (17.56)	< 0.001

eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; CON, controls; SD, standard deviation. A two-tailed independent t test or Mann–Whitney U test was used for the comparison of age and eGFR after the Kolmogorov–Smirnov test. The chi-square test was used for the comparison of percentage data

renal function were recruited to investigate the associations of plasma Aβ and tau levels with renal function. As shown in Table 1, there was no significant difference in the comorbidities of hypertension, diabetes, and hyperlipidemia between groups. As expected, the eGFR of CKD patients was lower than that of controls (23.57 ± 17.56 mL/min/1.73 m^2 vs. 124.1 ± 19.95 mL/min/1.73 m^2, p < 0.001). CKD patients had significantly higher plasma levels of Aβ40 (245.9 ± 209.5 pg/ml vs. 65.44 ± 66.51 pg/ml, p < 0.001) and Aβ42 (15.57 ± 14.86 pg/ml vs. 3.01 ± 3.06 pg/ml, p < 0.001) than controls (Fig. 1A and B). Moreover, plasma T-tau levels were also increased in CKD patients (14.59 ± 10.54 pg/ml vs. 6.37 ± 4.59 pg/ml, p < 0.001) (Fig. 1C).

Correlations of Plasma Aβ and tau Levels with Renal Function

Then, we analyzed the correlations of plasma Aβ and tau levels with eGFR adjusted for age and sex. As shown in Fig. 1D-F, plasma Aβ levels were negatively correlated with eGFR in both the CKD group (Aβ40: r = -0.570, p < 0.001; Aβ42: r = -0.560, p < 0.001) and all subjects (Aβ40: r = -0.607, p < 0.001; Aβ42: r = -0.577, p < 0.001) but not in the control group (Aβ40: r = -0.102, p = 0.540; Aβ42: r = 0.048, p = 0.786). In addition, plasma T-tau levels were also negatively correlated with eGFR in CKD patients (r = -0.461, p = 0.003), controls (r = -0.376, p = 0.020) and all subjects (r = -0.533, p < 0.001).

Decrease in CSF Aβ and Increase in CSF Tau/Aβ42 Levels in CKD Patients

To further reveal the relationships between renal function and brain AD-type pathologies, we evaluated another group of CKD patients and controls and collected CSF samples. The demographic characteristics of the participants are

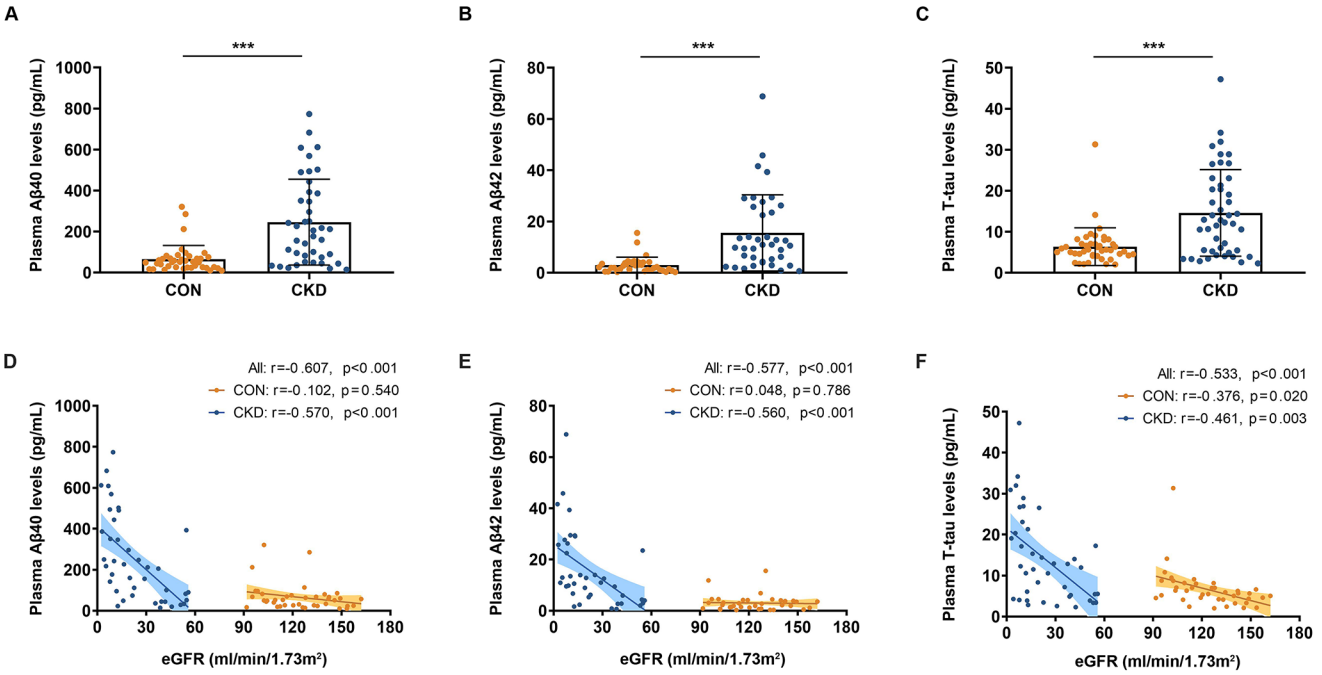

Fig. 1 Comparisons and correlations of plasma Aβ and tau levels in the participants. **A-C** Comparisons of plasma Aβ40, Aβ42 and T-tau levels between the controls and patients with CKD. **D-F** Correlations of eGFR with plasma Aβ40, Aβ42 and T-tau levels in subjects with CKD, controls, and all subjects. eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; CON, controls; T-tau, total tau. *** denotes p < 0.001. Partial correlation analyses were adjusted by age and sex. The shaded areas represent the 95% confidence intervals

Table 2 Characteristics of the participants with CSF samples

Characteristics	CON (n = 150)	CKD (n = 42)	*p* value
Age, mean (SD), y	70.11 (6.51)	72.57 (8.05)	0.104
Female, n (%)	47 (31.33)	13 (30.95)	0.963
Education level, mean (SD), y	9.17(2.64)	8.64(2.58)	0.207
APOE ε4 genotype, n (%)	18(12.00)	9 (21.43)	0.120
Hypertension, n (%)	48 (32.00)	16 (38.10)	0.459
Diabetes, n (%)	24 (16.00)	8(19.05)	0.640
Dyslipidemia, n (%)	55 (36.67)	17 (40.48)	0.652
eGFR, mean (SD), (mL/min/1.73m^2)	138.5 (26.91)	73.81 (15.95)	< 0.001
MMSE scores, mean (SD)	26.41 (1.88)	25.81 (2.16)	0.242

eGFR, estimated glomerular filtration rate; CSF, cerebrospinal fluid; T-tau, total tau; CKD, chronic kidney disease; APOE, apolipoprotein E; MMSE, Mini-Mental State Examination; SD, standard deviation. A two-tailed independent t test or Mann–Whitney U test was used for the comparison of age and eGFR after the Kolmogorov–Smirnov test. The chi-square test was used for the comparison of percentage data

shown in Table 2. There were no significant differences in age, sex, education level, comorbidities, APOE ε4 genotype or MMSE scores between groups. CKD patients had significantly lower levels of eGFR than controls (73.81 ± 15.95 mL/min/1.73 m^2 vs. 138.5 ± 26.91 mL/min/1.73 m^2, p < 0.001).

As shown in Fig. 2A-B, CSF levels of Aβ40 (11,595 ± 5629 pg/ml vs. 13,362 ± 3734 pg/ml, p = 0.020) and Aβ42 (1248 ± 518.9 pg/ml vs. 1557 ± 420.7 pg/ml, p < 0.001) were significantly decreased in CKD patients compared with controls. Although there was no significant difference in CSF P-tau levels between groups (48.78 ± 17.34 pg/ml vs. 46.36 ± 15.06 pg/ml, p = 0.374), the CSF T-tau levels showed an increasing trend in patients with CKD (225.9 ± 95.71 pg/ml vs. 194.1 ± 78.17 pg/ml, p = 0.063) (Fig. 2C-D). Additionally, CKD patients had significantly higher levels of CSF T-tau/Aβ42 (0.22 ± 0.15 vs. 0.14 ± 0.074, p < 0.001) and P-tau/Aβ42 (0.046 ± 0.027 vs. 0.032 ± 0.016, p = 0.001) than controls (Fig. 2E-F).

Correlations of CSF AD Biomarkers with Renal Function

Partial correlation analyses adjusted for age, sex and APOE ε4 genotype were used to analyze the correlations of CSF AD biomarkers with eGFR. No correlations of eGFR with CSF Aβ40 (CKD patients: r = 0.179, p = 0.297; controls: r = -0.063, p = 0.457; all participants: r = 0.107, p = 0.151) or Aβ42 (CKD patients: r = -0.126, p = 0.486; controls: r = -0.095, p = 0.255; all participants: r = 0.103, p = 0.170) levels were found (Fig. 3A-B). CSF T-tau levels were negatively correlated with eGFR in all subjects (r = -0.145, p = 0.048), and CSF P-tau levels were negatively correlated

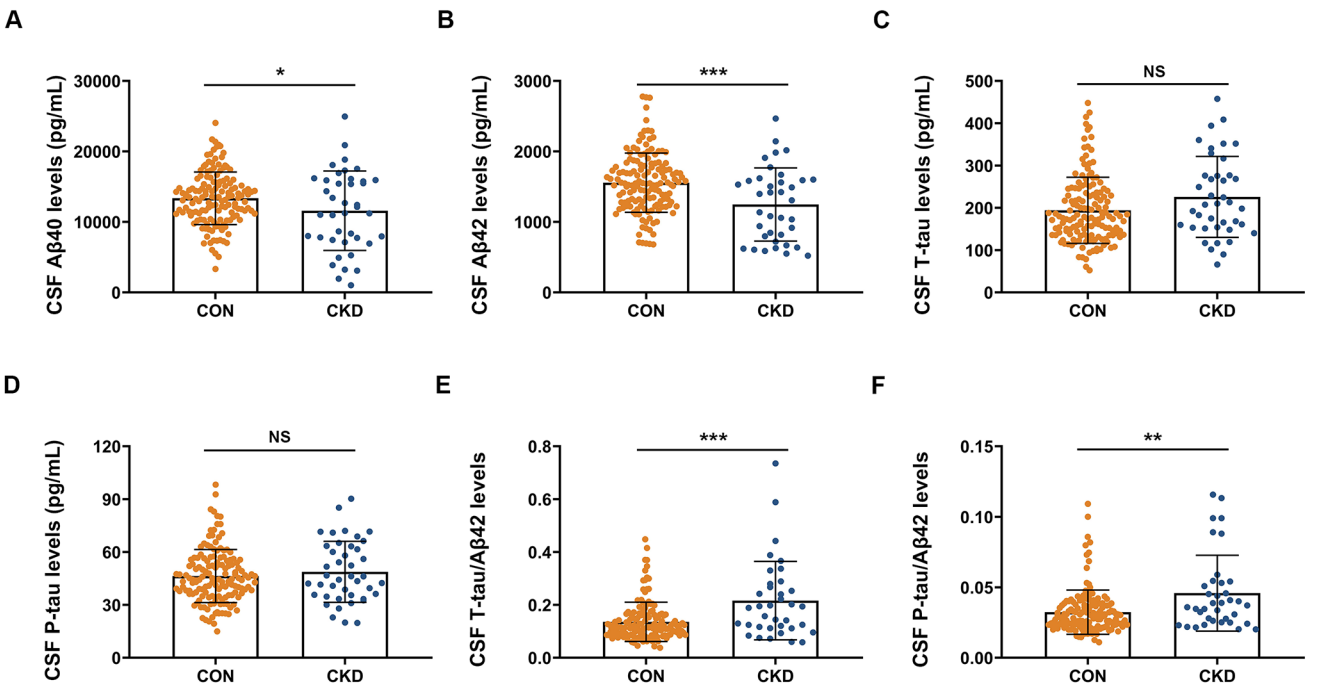

Fig. 2 Comparisons of CSF Aβ40, Aβ42, T-tau, P-tau, T-tau/Aβ42 and P-tau/Aβ42 levels between subjects with CKD and controls. eGFR, estimated glomerular filtration rate; CSF, cerebrospinal fluid; T-tau, total tau; P-tau, phosphorylated tau-181. * denotes p < 0.05, ** denotes p < 0.01, *** denotes p < 0.001. NS denotes no statistical significance

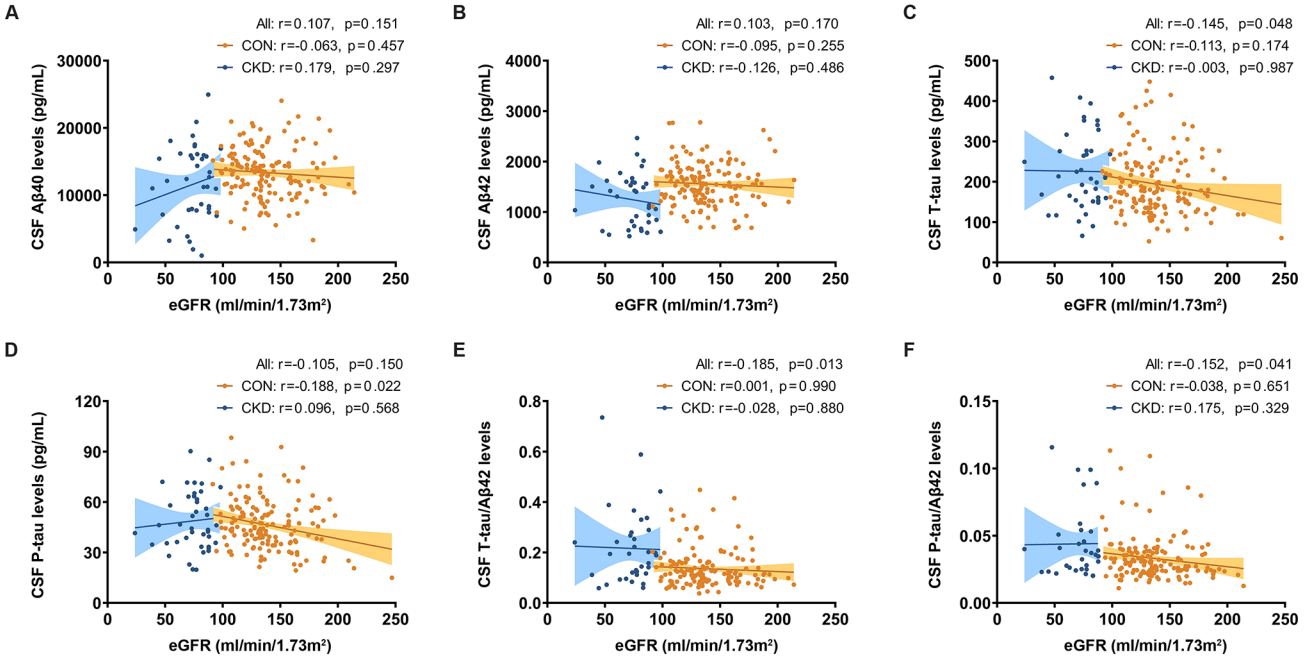

Fig. 3 Correlations of eGFR with the CSF Aβ40, Aβ42, T-tau, P-tau, T-tau/Aβ42 and P-tau/Aβ42 levels in subjects with CKD, controls, and all subjects. eGFR, estimated glomerular filtration rate; CSF, cerebrospinal fluid; T-tau, total tau; P-tau, phosphorylated tau-181. Partial correlation analyses were adjusted by age, sex and APOE ε4 genotype. The shaded areas represent the 95% confidence intervals

Table 3 Correlations of MMSE scores with eGFR in subjects with CKD, controls, and all subjects

		MMSE scores			
		Unadjusted [a]		Adjusted [b]	
		r	*p* value	r	*p* value
ALL (n = 192)	0.211	0.003		0.190	0.009
CON (n = 150)	0.202	0.013		0.228	0.006
CKD (n = 42)	0.061	0.702		0.005	0.974

[a] Spearman correlation analyses were used to examine the correlations of eGFR with MMSE scores

[b] Partial correlation analyses were adjusted by age, sex, ε4 genotype and education level

Abbreviations: ALL, all participants; eGFR, estimated glomerular filtration rate; MMSE, Mini-Mental State Examination; CKD, chronic kidney disease; CON, controls

with eGFR in controls (r = -0.188, p = 0.022) (Fig. 3C-D). As previous studies indicate that the ratio of P-tau to Aβ42 can reflect cerebral Aβ pathology to some extent [18], we further analyzed the correlations of CSF tau/Aβ42 with eGFR. eGFR was negatively correlated with CSF T-tau/Aβ42 (r = -0.185, p = 0.013) and P-tau/Aβ42 (r = -0.152, p = 0.041) in all subjects (Fig. 3E-F). However, there was no correlation between CSF tau/Aβ42 levels and eGFR in CKD patients (T-tau/Aβ42: r = -0.028, p = 0.880; P-tau/Aβ42: r = 0.175, p = 0.329) or controls (T-tau/Aβ42: r = 0.001, p = 0.990; P-tau/Aβ42: r = -0.038, p = 0.651).

Correlations of MMSE Scores with Renal Function

Finally, we examined the correlations of eGFR with cognitive function. As shown in Table 3, MMSE scores were positively correlated with eGFR in controls (r = 0.202, p = 0.013) and all participants (r = 0.211, p = 0.003). These correlations remained significant after adjusting for age, sex, APOE ε4 genotype and education level. No correlation of the MMSE scores with eGFR was found in CKD patients regardless of adjusting for confounders. These findings further indicate that cognitive status may decrease with renal insufficiency.

Discussion

Our study showed that CKD patients had higher levels of Aβ and T-tau in plasma and lower levels of Aβ and higher levels of T-tau/Aβ42 and P-tau/Aβ42 in CSF. Both plasma Aβ and T-tau levels were negatively correlated with eGFR.

In addition, we found that eGFR was negatively correlated with CSF levels of T-tau, T-tau/Aβ42 and P-tau/Aβ42 but positively correlated with cognitive function. These results suggest that renal function may be involved in the pathogenesis of AD.

Previous investigations have indicated that the clearance of Aβ and tau beyond the brain plays critical roles in the progression of AD [19–21]. It is estimated that 40–60% of Aβ and approximately 19% of tau from the brain is cleared through transport to the periphery [5, 8, 22, 23]. As the major excretory organs, the kidneys may play an important role in the clearance of AD pathogenic peptides. Radioactivity can be detected in the kidneys after injecting radioactive iodine-labeled Aβ or tau into the brain [5, 8]. In addition, an animal study showed that the serum Aβ levels in the renal artery are higher than those in the renal vein, which further supports the critical role of the kidneys in clearing Aβ [11]. Thus, CKD patients have increased Aβ levels in the blood compared with healthy patients [12]. Previous studies have shown that tau can be cleared by peripheral organs, including the kidneys, in animals [5], but the detailed mechanism remains unknown. Our study provides clinical evidence for the roles of the kidneys in the clearance of peripheral Aβ as well as tau.

Although several studies have demonstrated the associations of renal function with blood Aβ and tau in CKD [12, 24], it remains unknown whether renal function are related to CSF levels of Aβ and tau, which could represent brain AD pathology. According to a systemic view of AD pathogenesis, abnormal metabolism of Aβ in the periphery can aggravate brain AD pathology [6, 25, 26]. In this study, we found that renal function may be related to brain Aβ deposition, as reflected by decreased CSF Aβ and increased CSF P-tau/Aβ42 in CKD patients. This further confirmed the systemic view of AD. In light of the Aβ cascade hypothesis, the increase in cerebral Aβ levels caused by renal failure can further induce the hyperphosphorylation of tau [11, 27, 28]. In addition, the decrease in GFR can impair aluminum excretion, which could lead to increased levels of p-tau in the CSF and AD-related pathological changes [29, 30]. Consequently, renal insufficiency may affect AD-related Aβ and tau pathology in the brain.

There are several theories linking chronic kidney failure to cognitive impairment, including the kidney-brain-axis theory [31]. Our study showed that MMSE scores decreased with lower eGFR values. Previous studies have also shown that a metabolic imbalance of homocysteine caused by CKD plays an important role in the pathogenesis of AD through the activation of oxidative stress [32, 33]. Massive accumulation of uremic toxins occurs due to renal insufficiency, and these toxins exert neurotoxic effects and aggravate cognitive impairment [34]. Moreover, the disturbance of angiotensin II in chronic kidney failure also promotes brain damage in AD [35, 36]. As a result, patients with CKD are more prone to hypomnesia and AD comorbidities [14]. Epidemiological investigation reported that lower eGFR was associated with a higher risk of dementia [15, 37, 38]. A postmortem study showed that patients with impaired kidney function had a higher risk of AD dementia and a higher burden of cerebral amyloid angiopathy [39]. However, a cohort study in Germany noted that impaired kidney function was associated with higher blood neurofilament and p-tau181 levels but not with AD or all-cause dementia risk [24]. As the author discussed in the limitations, the participants in this study were younger at baseline, the incidence of dementia was comparatively low, and the clinical diagnoses of dementia in this study may have resulted in misdiagnosis or underdiagnosis, which may partially explain the inconsistent results compared with previous studies. It showed that lower eGFR was associated with a reduction in cortical brain volume, although eGFR-related brain atrophy was not selective for regions typically affected by AD [40]. This study suggests that AD may not be a leading factor in the development of brain pathologies related to CKD but may coexist with vascular etiologies of reduced brain volume, but this needs to be further investigated in additional studies. Therefore, our study not only confirms the relationships of renal dysfunction with cognitive impairment in elderly individuals but also provides clinical evidence that renal dysfunction is related to brain AD-type pathological changes.

Our results also bring attention to the diagnostic efficiency of p-tau in the periphery. Recent studies have found that pathological changes in the brains of AD patients can be reflected by plasma P-tau217 and P-tau181 levels, which show excellent diagnostic performance [41, 42]. However, the above research noted that renal insufficiency may affect AD diagnosis based on levels of plasma P-tau. We further provided evidence for this issue. Thus, adjusting for renal function is needed for early diagnosis of AD based on plasma P-tau levels in the future.

It is noteworthy that we were unable to determine causality for the relationship between renal function and changes in AD biomarkers due to the cross-sectional design of our study. Longitudinal studies including more CKD patients with eGFR < 30 mL/min/1.73 m^2 should be carried out to better clarify the relationships between renal failure and brain AD-type pathologies and cognitive impairment in the future. Dialysis is an effective measure to treat renal failure. The peripheral levels of Aβ in patients with CKD can be effectively reduced after hemodialysis or peritoneal dialysis [12, 43]. Hemodialysis was also found to reduce Aβ deposition in the brains of AD patients [44]. However, whether dialysis decreases the burden of cerebral Aβ and tau and

improves symptoms of cognitive decline in CKD and AD patients remains to be further studied.

In summary, our study found that the decline in renal function was correlated with cognitive decline and abnormal AD biomarker levels in plasma as well as CSF. This study provides human evidence that renal function may be involved in the pathogenesis of AD, further indicating that AD may be a systemic disease.

Acknowledgements Not applicable.

Author Contributions X-LB and Y-JW conceived and designed the project, X-QY, LL, Y-DB, G-HZ, A-YS and Y-HL performed biomarker testing and clinical data collection. H-LS, X-QY, W-SJ, JL and LZ analyzed the data. H-LS and X-LB wrote the article. All authors contributed to the article and approved the submitted version.

Funding This study was supported by the National Natural Science Foundation of China (Grant no. 82101499 and 82122023).

Data Availability The data of this study are available from the corresponding author with a reasonable request.

Declarations

Ethics Approval The study was approved by the Institutional Review Board of Daping Hospital, Chongqing, China.

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

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

Competing Interests The authors declare no competing or other conflicts of interests.

Conflict of interest None.

References

1. 2021 Alzheimer's disease facts and Fig. (2021) Alzheimer's Dement 17(3):327–406. https://doi.org/10.1002/alz.12328
2. Long JM, Holtzman DM (2019) Alzheimer Disease: an update on pathobiology and treatment strategies. Cell 179(2):312–339. https://doi.org/10.1016/j.cell.2019.09.001
3. Huang S, Wang Y-J, Guo J (2022) Biofluid biomarkers of Alzheimer's disease: progress, problems, and perspectives. Neurosci Bull 38(6):677–691. https://doi.org/10.1007/s12264-022-00836-7
4. Chen S-H, He C-Y, Shen Y-Y, Zeng G-H, Tian D-Y, Cheng Y, Xu M-Y, Fan D-Y, Tan C-R, Shi A-Y, Bu X-L, Wang Y-J (2022) Polysaccharide Krestin prevents Alzheimer's Disease-type Pathology and Cognitive deficits by enhancing monocyte Amyloid-β Processing. Neurosci Bull 38(3):290–302. https://doi.org/10.1007/s12264-021-00779-5
5. Wang J, Jin W-S, Bu X-L, Zeng F, Huang Z-L, Li W-W, Shen L-L, Zhuang Z-Q, Fang Y, Sun B-L, Zhu J, Yao X-Q, Zeng G-H, Dong Z-F, Yu J-T, Hu Z, Song W, Zhou H-D, Jiang J-X, Liu Y-H, Wang Y-J (2018) Physiological clearance of tau in the periphery and its therapeutic potential for tauopathies. Acta Neuropathol 136(4):525–536. https://doi.org/10.1007/s00401-018-1891-2
6. Wang J, Gu BJ, Masters CL, Wang Y-J (2017) A systemic view of Alzheimer disease — insights from amyloid-β metabolism beyond the brain. Nat Reviews Neurol 13(10):612–623. https://doi.org/10.1038/nrneurol.2017.111
7. Dugger BN, Hoffman BR, Scroggins A, Serrano GE, Adler CH, Shill HA, Belden CM, Sabbagh MN, Caviness JN, Driver Dunckley E, Beach TG (2019) Tau immunoreactivity in peripheral tissues of human aging and select tauopathies. Neurosci Lett 696:132–139. https://doi.org/10.1016/j.neulet.2018.12.031
8. Xiang Y, Bu X-L, Liu Y-H, Zhu C, Shen L-L, Jiao S-S, Zhu X-Y, Giunta B, Tan J, Song W-H, Zhou H-D, Zhou X-F, Wang Y-J (2015) Physiological amyloid-beta clearance in the periphery and its therapeutic potential for Alzheimer's disease. Acta Neuropathol 130(4):487–499. https://doi.org/10.1007/s00401-015-1477-1
9. Sun HL, Chen SH, Yu ZY, Cheng Y, Tian DY, Fan DY, He CY, Wang J, Sun PY, Chen Y, Tan CR, Wang JP, Song W, Zhou HD, Chen XW, Hu ZA, Bu XL, Wang YJ (2021) Blood cell-produced amyloid-beta induces cerebral Alzheimer-type pathologies and behavioral deficits. Mol Psychiatry 26(10):5568–5577. https://doi.org/10.1038/s41380-020-0842-1
10. Cheng Y, Jian J-M, He C-Y, Ren J-R, Xu M-Y, Jin W-S, Tan C-R, Zeng G-H, Shen Y-Y, Chen D-W, Li H-Y, yi X, Zhang Y, Zeng F, Wang Y-J (2022) The correlations of plasma liver-type fatty acid-binding protein with Amyloid-β and tau levels in patients with Alzheimer's Disease. J Alzheimers Dis 88:1–9. https://doi.org/10.3233/JAD-220126
11. Tian D-Y, Cheng Y, Zhuang Z-Q, He C-Y, Pan Q-G, Tang M-Z, Hu X-L, Shen Y-Y, Wang Y-R, Chen S-H, Sun H-L, Sun P-Y, Yu Z-Y, Fan D-Y, Bu X-L, Tan C-R, Zeng G-H, Wang J, Zhao H-W, Wang Y-J (2021) Physiological clearance of amyloid-beta by the kidney and its therapeutic potential for Alzheimer's disease. Mol Psychiatry 26(10):6074–6082. https://doi.org/10.1038/s41380-021-01073-6
12. Liu YH, Xiang Y, Wang YR, Jiao SS, Wang QH, Bu XL, Zhu C, Yao XQ, Giunta B, Tan J, Zhou HD, Wang YJ (2015) Association between serum amyloid-Beta and renal functions: implications for roles of kidney in amyloid-Beta clearance. Mol Neurobiol 52(1):115–119. https://doi.org/10.1007/s12035-014-8854-y
13. Gronewold J, Klafki H-W, Baldelli E, Kaltwasser B, Seidel UK, Todica O, Volsek M, Haußmann U, Wiltfang J, Kribben A, Bruck H, Hermann DM (2016) Factors responsible for plasma β-Amyloid Accumulation in chronic kidney disease. Mol Neurobiol 53(5):3136–3145. https://doi.org/10.1007/s12035-015-9218-y
14. Zhang C-Y, He F-F, Su H, Zhang C, Meng X-F (2020) Association between chronic kidney disease and Alzheimer's disease: an update. Metab Brain Dis 35(6):883–894. https://doi.org/10.1007/s11011-020-00561-y
15. Hong X, Sara G-P, Marco T, Marie E, Bengt L, Maria E, Juan Jesus C (2021) Kidney function, kidney function decline, and the risk of dementia in older adults. Neurology 96(24):e2956. https://doi.org/10.1212/WNL.0000000000012113
16. Stevens PE, Levin A (2013) Evaluation and management of chronic kidney disease: Synopsis of the kidney disease: improving global outcomes 2012 clinical practice Guideline. Ann Intern Med 158(11):825–830. https://doi.org/10.7326/0003-4819-158-11-201306040-00007
17. Xie P, Huang J-M, Lin H-y, Wu W-J, Pan L-P (2013) CDK-EPI equation may be the most proper formula based on creatinine in determining glomerular filtration rate in chinese patients with chronic kidney disease. Int Urol Nephrol 45(4):1057–1064. https://doi.org/10.1007/s11255-012-0325-7
18. Hansson O, Seibyl J, Stomrud E, Zetterberg H, Trojanowski JQ, Bittner T, Lifke V, Corradini V, Eichenlaub U, Batrla R, Buck K,

Zink K, Rabe C, Blennow K, Shaw LM (2018) CSF biomarkers of Alzheimer's disease concord with amyloid-β PET and predict clinical progression: a study of fully automated immunoassays in BioFINDER and ADNI cohorts. Alzheimer's Dement 14(11):1470–1481. https://doi.org/10.1016/j.jalz.2018.01.010

19. Cheng Y, Tian D-Y, Wang Y-J (2020) Peripheral clearance of brain-derived Aβ in Alzheimer's disease: pathophysiology and therapeutic perspectives. Translational Neurodegeneration 9(1):16. https://doi.org/10.1186/s40035-020-00195-1
20. Xin S-H, Tan L, Cao X, Yu J-T, Tan L (2018) Clearance of amyloid Beta and tau in Alzheimer's Disease: from Mechanisms to Therapy. Neurotox Res 34(3):733–748. https://doi.org/10.1007/s12640-018-9895-1
21. Liu Z-H, Wang Y-J, Bu X-L (2023) Alzheimer's disease: targeting the peripheral circulation. Mol Neurodegeneration 18(1):3. https://doi.org/10.1186/s13024-023-00594-8
22. Yuede CM, Lee H, Restivo JL, Davis TA, Hettinger JC, Wallace CE, Young KL, Hayne MR, Bu G, Li CZ, Cirrito JR (2016) Rapid in vivo measurement of beta-amyloid reveals biphasic clearance kinetics in an Alzheimer's mouse model. J Exp Med 213(5):677–685. https://doi.org/10.1084/jem.20151428
23. Roberts KF, Elbert DL, Kasten TP, Patterson BW, Sigurdson WC, Connors RE, Ovod V, Munsell LY, Mawuenyega KG, Miller-Thomas MM, Moran CJ, Cross Iii DT, Derdeyn CP, Bateman RJ (2014) Amyloid-β efflux from the central nervous system into the plasma. Ann Neurol 76(6):837–844. https://doi.org/10.1002/ana.24270
24. Stocker H, Beyer L, Trares K, Perna L, Rujescu D, Holleczek B, Beyreuther K, Gerwert K, Schöttker B, Brenner H (2023) Association of kidney function with development of Alzheimer Disease and other dementias and dementia-related blood biomarkers. JAMA Netw open 6:e2252387. https://doi.org/10.1001/jamanetworkopen.2022.52387
25. Bu XL, Xiang Y, Jin WS, Wang J, Shen LL, Huang ZL, Zhang K, Liu YH, Zeng F, Liu JH, Sun HL, Zhuang ZQ, Chen SH, Yao XQ, Giunta B, Shan YC, Tan J, Chen XW, Dong ZF, Zhou HD, Zhou XF, Song W, Wang YJ (2018) Blood-derived amyloid-β protein induces Alzheimer's disease pathologies. Mol Psychiatry 23(9):1948–1956. https://doi.org/10.1038/mp.2017.204
26. Sun H-L, Chen S-H, Yu Z-Y, Cheng Y, Tian D-Y, Fan D-Y, He C-Y, Wang J, Sun P-Y, Chen Y, Tan C-R, Wang J-P, Song W, Zhou H-D, Chen X-W, Hu Z-A, Bu X-L, Wang Y-J (2021) Blood cell-produced amyloid-β induces cerebral Alzheimer-type pathologies and behavioral deficits. Mol Psychiatry 26(10):5568–5577. https://doi.org/10.1038/s41380-020-0842-1
27. Zhang H, Wei W, Zhao M, Ma L, Jiang X, Pei H, Cao Y, Li H (2021) Interaction between Aβ and tau in the pathogenesis of Alzheimer's Disease. Int J Biol Sci 17(9):2181–2192. https://doi.org/10.7150/ijbs.57078
28. Hampel H, Hardy J, Blennow K, Chen C, Perry G, Kim SH, Villemagne VL, Aisen P, Vendruscolo M, Iwatsubo T, Masters CL, Cho M, Lannfelt L, Cummings JL, Vergallo A (2021) The Amyloid-β pathway in Alzheimer's Disease. Mol Psychiatry 26(10):5481–5503. https://doi.org/10.1038/s41380-021-01249-0
29. Harrington CR, Wischik CM, McArthur FK, Taylor GA, Edwardson JA, Candy JM (1994) Alzheimer's-disease-like changes in tau protein processing: association with aluminium accumulation in brains of renal dialysis patients. The Lancet 343(8904):993–997. https://doi.org/10.1016/S0140-6736(94)90124-4
30. Shin RW, Lee VM, Trojanowski JQ (1994) Aluminum modifies the properties of Alzheimer's disease PHF tau proteins in vivo and in vitro. The Journal of Neuroscience 14 (11):7221.https://doi.org/10.1523/JNEUROSCI.14-11-07221.1994
31. Kelly DM, Rothwell PM (2022) Disentangling the relationship between chronic kidney Disease and Cognitive Disorders. Front Neurol 13:830064. https://doi.org/10.3389/fneur.2022.830064
32. O K, Siow LY (2018) Metabolic imbalance of homocysteine and hydrogen sulfide in kidney disease. Curr Med Chem 25(3):367–377. https://doi.org/10.2174/0929867324666170509145240
33. Kowalska M, Wize K, Prendecki M, Lianeri M, Kozubski W, Dorszewska J (2020) Genetic variants and oxidative stress in Alzheimer's Disease. Curr Alzheimer Res 17(3):208–223. https://doi.org/10.2174/1567205017666200224121447
34. Shi Y, Liu Z, Shen Y, Zhu H (2018) A novel perspective linkage between kidney function and Alzheimer's Disease. Front Cell Neurosci 12:384. https://doi.org/10.3389/fncel.2018.00384
35. Nakagawa T, Hasegawa Y, Uekawa K, Kim-Mitsuyama S (2017) Chronic kidney disease accelerates cognitive impairment in a mouse model of Alzheimer's disease, through angiotensin II. Exp Gerontol 87:108–112. https://doi.org/10.1016/j.exger.2016.11.012
36. Ribeiro TV, de Souza CL, Simões e Silva CA (2020) Renin-angiotensin system and Alzheimer's Disease Pathophysiology: from the potential interactions to therapeutic perspectives. Protein & Peptide Letters 27(6):484–511. https://doi.org/10.2174/0929866527666191230103739
37. Scheppach JB, Coresh J, Wu A, Gottesman RF, Mosley TH, Knopman DS, Grams ME, Sharrett AR, Koton S (2020) Albuminuria and estimated GFR as risk factors for dementia in midlife and older age: findings from the ARIC Study. Am J kidney diseases: official J Natl Kidney Foundation 76(6):775–783. https://doi.org/10.1053/j.ajkd.2020.03.015
38. Chi HC, Liu Y, Tan CC, Zhang YC, Tan L, Xu W (2023) Adult renal dysfunction and risk of Dementia or Cognitive decline: brain-kidney Axis Hypothesis based on a systematic review and Meta-analysis. J Prev Alzheimer's Disease. https://doi.org/10.14283/jpad.2023.35
39. Wang S, Wang J, Dove A, Guo J, Yang W, Qi X, Bennett DA, Xu W (2022) Association of impaired kidney function with dementia and brain pathologies: a community-based cohort study. Alzheimer's & Dementia. https://doi.org/10.1002/alz.12910. n/a (n/a)
40. Scheppach J, Wu A, Gottesman R, Mosley T, Arsiwala L, Knopman D, Grams M, Sharrett A, Coresh J, Koton S (2022) Association of kidney function measures with Signs of Neurodegeneration and Small Vessel Disease on Brain magnetic resonance imaging: the atherosclerosis risk in Communities (ARIC) Study. Am J Kidney Dis 81. https://doi.org/10.1053/j.ajkd.2022.07.013
41. Thijssen EH, La Joie R, Strom A, Fonseca C, Iaccarino L, Wolf A, Spina S, Allen IE, Cobigo Y, Heuer H, VandeVrede L, Proctor NK, Lago AL, Baker S, Sivasankaran R, Kieloch A, Kinhikar A, Yu L, Valentin M-A, Jeromin A, Zetterberg H, Hansson O, Mattsson-Carlgren N, Graham D, Blennow K, Kramer JH, Grinberg LT, Seeley WW, Rosen H, Boeve BF, Miller BL, Teunissen CE, Rabinovici GD, Rojas JC, Dage JL, Boxer AL (2021) Plasma phosphorylated tau 217 and phosphorylated tau 181 as biomarkers in Alzheimer's disease and frontotemporal lobar degeneration: a retrospective diagnostic performance study. Lancet Neurol 20(9):739–752. https://doi.org/10.1016/S1474-4422(21)00214-3
42. Mielke MM, Dage JL, Frank RD, Algeciras-Schimnich A, Knopman DS, Lowe VJ, Bu G, Vemuri P, Graff-Radford J, Jack CR, Petersen RC (2022) Performance of plasma phosphorylated tau 181 and 217 in the community. Nat Med 28(7):1398–1405. https://doi.org/10.1038/s41591-022-01822-2
43. Kitaguchi N, Tatebe H, Sakai K, Kawaguchi K, Matsunaga S, Kitajima T, Tomizawa H, Kato M, Sugiyama S, Suzuki N, Mizuno M, Takechi H, Nakai S, Hiki Y, Kushimoto H, Hasegawa M, Yuzawa Y, Tokuda T (2019) Influx of tau and Amyloid-β proteins into the blood during Hemodialysis as a therapeutic extracorporeal blood Amyloid-β removal system for Alzheimer's Disease. J Alzheimers Dis 69:1–21. https://doi.org/10.3233/JAD-190087

44. Sakai K, Senda T, Hata R, Kuroda M, Hasegawa M, Kato M, Abe M, Kawaguchi K, Nakai S, Hiki Y, Yuzawa Y, Kitaguchi N (2016) Patients that have undergone Hemodialysis exhibit lower amyloid deposition in the brain: evidence supporting a therapeutic strategy for Alzheimer's disease by removal of blood amyloid. J Alzheimers Dis 51:997–1002. https://doi.org/10.3233/JAD-151139