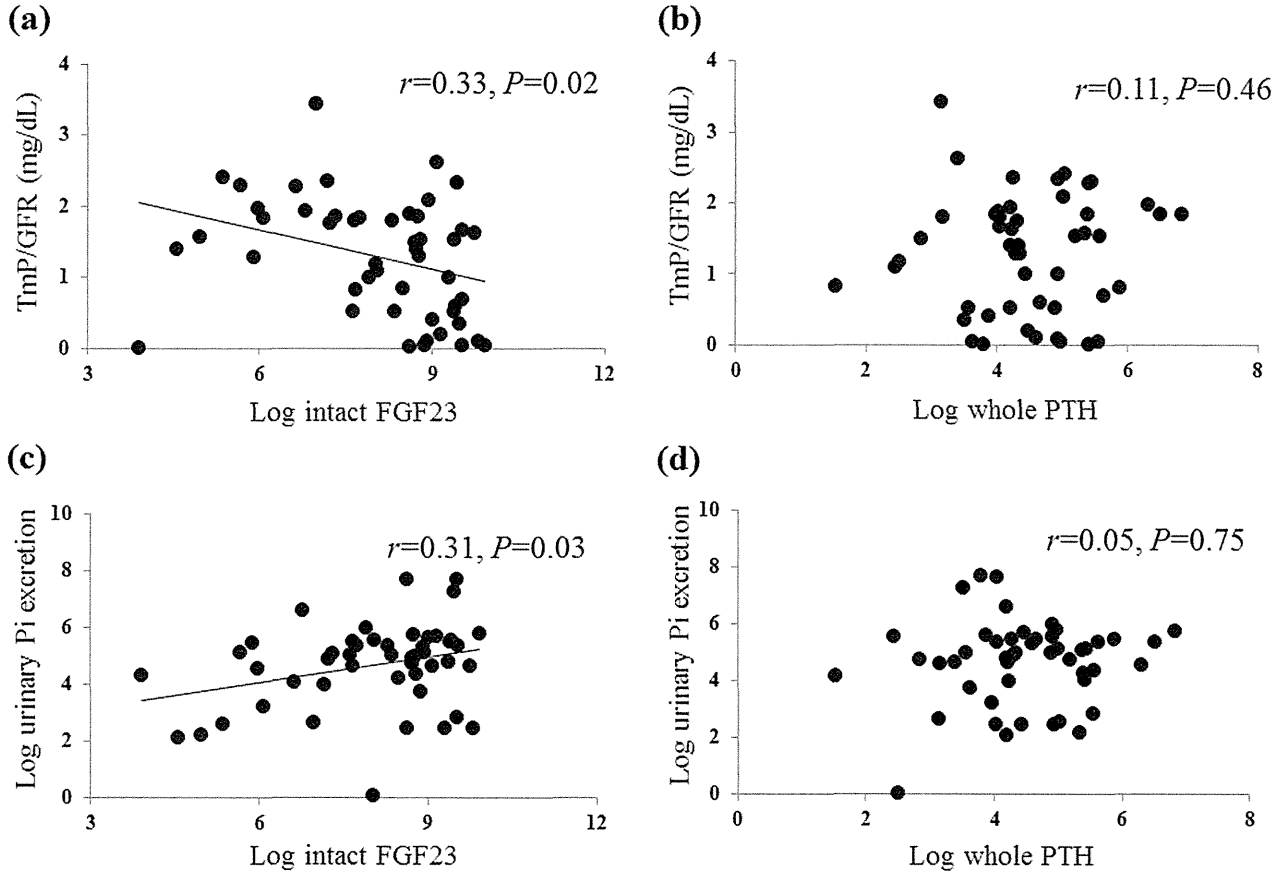

FIG. 1. Correlation between TmP/GFR, urinary Pi excretion, and levels of phosphaturic hormones. Correlation between TmP/GFR and (A) serum fibroblast growth factor 23 (FGF23) or (B) serum whole parathyroid hormone (PTH) and between urinary Pi excretion and (C) serum FGF23 or (D) serum whole PTH. R^2 indicates the coefficient of determination. Serum FGF23 and PTH levels were both transformed into logarithmic values to improve their skewed distributions. $P < 0.05$ was considered to be statistically significant.

with neither TmP/GFR nor log urinary Pi excretion (Fig. 1).

Multivariate linear regression analysis of TmP/GFR

The univariate regression analysis showed that log TmP/GFR was significantly ($P < 0.05$) and negatively correlated with log serum FGF23, body mass index, and PD volume, while other potential confounders, including log serum whole PTH, were not (Table 2). Multivariate linear regression analysis showed that log serum FGF23 was significantly ($P < 0.05$) negatively correlated with log TmP/GFR, even after adjusting for body mass index and peritoneal Cr clearance (Table 2). However, there was no significant correlation between log serum whole PTH and log TmP/GFR.

Multivariate linear regression analysis of the total urinary Pi excretion

Univariate regression analysis showed that log total urinary Pi excretion was significantly ($P < 0.05$) and positively associated with the log serum FGF23, serum Pi level, PD volume, and renal Cr clearance (Table 3). Multivariate linear regression analysis showed that log serum FGF23 was significantly ($P < 0.05$) positively correlated with log total urinary Pi excretion, even after adjusting for potential confounders, including estimated Pi intake, PD volume, and renal Cr clearance (Table 3). However, there was no significant correlation between log serum whole PTH and log total urinary Pi excretion. Importantly, the standardized β-coefficient of renal Cr clearance was approximately twofold larger than that of the serum FGF23 level.

Relationship between serum FGF23 level and peritoneal Pi excretion

Univariate regression analysis showed that estimated Pi intake, PD volume, peritoneal ultrafiltration volume, D/P Cr, serum Pi level, and log serum FGF23 were significantly ($P < 0.05$) associated with log total peritoneal Pi excretion (Table 4). Multivariate linear regression analysis showed that the estimated

TABLE 2. *Multivariate regression model for TmP/GFR*

Variates	Univariate model		Multivariate model		
	β-coefficient	*P*-value	*β*-coefficient	*Standardized β*-coefficient	*P*-value
Age, per 10 years increase	−0.095	0.17			
Sex (male)	−0.341	0.17			
Underlying kidney disease (diabetes mellitus)	−0.283	0.34			
Dialysis vintage, per 100 day increase	−0.013	0.11			
nPCR, per 1 g/kg per day increase	0.648	0.22			
Body mass index, per 1 kg/m^2 increase	−0.079	**0.04**	−0.080	−0.292	**0.04**
Estimated Pi intake, per 100 mg/day increase	−0.034	0.57			
Peritoneal dialysis volume, per 1 L increase	−0.076	0.07	0.015	−0.048	0.774
Serum calcium, per 1 mmol/L increase	−0.901	0.34			
Serum Pi, per 1 mmol/L increase	−0.009	0.98			
Log serum PTH, per 1 unit increase	0.037	0.75			
Log serum FGF23, per 1 unit increase	−0.184	**0.02**	−0.182	−0.329	**0.04**
Use of vitamin D receptor activator	−0.337	0.16			
Use of Pi-binder	−0.228	0.48			
Use of cinacalcet	−0.39	0.23			

Data for 52 patients. Variates showing a *P*-value of <0.1 in the univariate analysis were included in the multivariate analyses. A *P*-value of <0.05 was considered to be statistically significant. FGF23, fibroblast growth factor 23; nPCR, normalized protein catabolic rate; Pi, phosphate; PTH, parathyroid hormone. Bold faces indicate that the covariates are statistically significant.

Pi intake, D/P Cr, and serum Pi level were significantly ($P < 0.05$) associated with log total peritoneal Pi excretion, and peritoneal ultrafiltration volume and peritoneal dialysis volume were marginally and significantly associated with log total peritoneal Pi excretion (Table 4). However, neither log serum FGF23 nor log serum whole PTH was associated with log total urinary Pi excretion, indicating that total peritoneal Pi excretion was not dependent on the level of FGF23 or PTH.

DISCUSSION

The present study demonstrated that the serum FGF23 level, but not the serum PTH level, is significantly negatively associated with TmP/GFR and significantly positively associated with urinary Pi excretion, even after adjusting for potential confounders, in PD patients with RRF. This indicates that an increased level of circulating FGF23 inhibits transtubular Pi reabsorption and increases total

TABLE 3. *Multivariate regression model for log urinary Pi excretion*

Variates	Univariate model		Multivariate model		
	β-coefficient	*P*-value	*β*-coefficient	*Standardized β*-coefficient	*P*-value
Age, per 10 years increase	−0.080	0.44			
Sex (male)	0.426	0.25			
Underlying kidney disease (diabetes mellitus)	−0.474	0.27			
Dialysis vintage, per 100 day increase	−0.012	0.74			
nPCR, per 1 g/kg per day increase	0.935	0.23			
Body mass index, per 1 kg/m^2 increase	0.088	0.13			
Estimated Pi intake, per 100 mg/day increase	0.225	**<0.01**	0.160	0.288	0.09
Renal creatinine clearance, per 10 L/week increase	0.016	**<0.01**	0.152	0.569	**<0.01**
Peritoneal dialysis volume, per 1 L increase	−0.178	**<0.01**	−0.121	−0.276	**0.03**
Serum calcium, per 1 mmol/L increase	−1.751	0.20			
Serum Pi, per 1 mmol/L increase	0.071	0.89			
Log serum PTH, per 1 unit increase	0.033	0.57			
Log serum FGF23, per 1 unit increase	0.068	**0.04**	0.211	0.258	**0.04**
Use of vitamin D receptor activator	0.325	0.36			
Use of Pi-binder	−0.223	0.64			
Use of cinacalcet	−0.81	0.17			

Data for 52 patients. Variates showing a *P*-value of <0.1 in the univariate analysis were included in the multivariate analyses. A *P*-value of <0.05 was considered to be statistically significant. FGF23, fibroblast growth factor 23; nPCR, normalized protein catabolic rate; Pi, phosphate, PTH, parathyroid hormone. Bold faces indicate that the covariates are statistically significant.

TABLE 4. *Multivariate linear regression model for peritoneal Pi elimination*

Variates	Univariate model		Multivariate model		
	β-coefficient	*P*-value	β-coefficient	*Standardized* β-coefficient	*P*-value
Age, per 10 years increase	7.81	0.25			
Sex (male)	28.8	0.23			
Underlying kidney disease (diabetes mellitus)	22.5	0.37			
Dialysis vintage, per 100 day increase	1.95	0.40			
nPCR, per 1 g/kg per day increase	16.6	0.74			
BMI, per 1 kg/m^2 increase	9.3	0.15			
Estimated phosphate intake, per 1 mg/day increase	15.9	**<0.01**	0.096	0.238	**0.03**
Peritoneal dialysis volume, per 1 L increase	22.8	**<0.01**	8.44	0.233	0.10
D/P Cr, per 1 unit increase	227.6	**<0.01**	207.3	0.390	**<0.01**
Peritoneal ultrafiltration volume, per 100 mL increase	7.46	**<0.01**	2.76	0.183	0.07
Use of automated peritoneal dialysis	8.56	0.71			
Serum calcium, per 1 mmol/L increase	9.77	0.66			
Serum Pi, per 1 mmol/L increase	31.9	**<0.01**	22.8	0.317	**<0.01**
Log serum PTH, per 1 unit increase	−5.51	0.61			
Log serum FGF23, per 1 unit increase	18.3	**0.01**	0.637	0.012	0.91
Use of vitamin D receptor activator	−3.81	0.87			
Use of Pi-binder	42.7	0.16			
Use of cinacalcet	20.8	0.51			

Data for 52 patients. Variates showing a *P*-value of <0.1 in the univariate analysis were included in the multivariate analyses. A *P*-value of <0.05 was considered to be statistically significant. BMI, body mass index; Cr, creatinine; FGF23, fibroblast growth factor 23; nPCR, normalized protein catabolic rate; Pi, phosphate; PTH, parathyroid hormone. Bold faces indicate that the covariates are statistically significant.

urinary Pi excretion. Furthermore, the present study also suggests that FGF23 is more potent than PTH in regulating renal Pi excretion in PD patients with RRF.

Regulation of Na–Pi co-transporters in the renal proximal tubules by FGF23 and PTH plays a central role in the modulation of transtubular resorption of Pi in both healthy subjects and patients with mild to moderate CKD (4,5,7). However, the effects of these two phosphaturic hormones on TmP/GFR and urinary Pi excretion remain undetermined in advanced CKD patients. Based on the findings of the present study, serum FGF23 level, but not PTH level, is associated with TmP/GFR and total urinary Pi excretion. In this regard, the present study provides evidence that FGF23 and PTH exert different effects on urinary Pi excretion under conditions of advanced CKD. Indeed, our results are in accordance with those of a recent report showing that the serum FGF23 level is associated with tubular reabsorption of Pi in hemodialysis patients with residual urine, and contributes to a compensatory increase in urinary Pi excretion (18). In addition, a multivariate analysis revealed that the standardized β-coefficient of renal Cr clearance was approximately twofold greater than that of the serum FGF23 level. These results indicate that the contribution of FGF23 to urinary Pi excretion is relatively smaller than that of RRF, and that preserving RRF is the most important factor for maintaining Pi balance in PD patients (19).

There are several possible explanations for the decreased urinary Pi excretion in PD patients with RRF and a high serum FGF23 level. First, GFR is decreased in patients with low RRF status. Total urinary Pi excretion is determined by the balance between the amount of Pi filtered through the glomeruli and the amount of Pi reabsorbed at the proximal tubules (20). Therefore, a decrease in GFR can directly and largely influence total urinary Pi excretion. Second, the obligatory co-receptor Klotho is estimated to decrease in the low RRF state (21). Under these conditions, even if the serum FGF23 level is high, FGF23 signaling can be attenuated. Third, the intact tubulointerstitial system, including the expression of FGF receptor (FGFR) and Na–Pi co-transporter type II, the target of FGF23 and PTH, can be damaged or injured. This leads to inappropriate reabsorption of Pi in the proximal tubules, although the apical expression and trafficking system of Na–Pi co-transporter type II in the proximal tubules has not been investigated in patients with advanced CKD. However, another study reported evidence supporting the "intact nephron theory", even in patients with low GFR (22). Therefore, further studies are needed to clarify the mechanisms accounting for the attenuated phosphaturic effect of FGF23 under conditions of relatively low GFR.

The clinical significance of a highly elevated serum FGF23 level in PD patients remains the subject of debate. FGF23 requires the co-receptor Klotho to

bind to FGFR (23), therefore, FGF23 signaling via FGFR in PD patients is attenuated compared with that observed under physiological conditions. According to the results of the present study, the association between serum FGF23 level and urinary Pi excretion suggests that an elevated serum level of FGF23 is effective, at least with respect to urinary Pi elimination. By contrast, the detrimental effects of FGF23 have also been reported. A recent study showed that the administration of anti-FGF23 antibodies increases the serum calcitriol level in CKD rats (24). Another study reported that the direct infusion of concentrated FGF23 into the heart induces cardiomegaly in mice, indicating the possible harmful effects of FGF23 on the cardiovascular system (25). More recently, FGF23 was found to inhibit the synthesis of calcitriol in peripheral macrophages (26). Given the importance of the local synthesis of calcitriol and the survival benefits of administering vitamin D receptor activators, FGF23 may exert harmful effects by inhibiting local calcitriol synthesis (27,28). Based on its possible harmful effects, some researchers regard an increased serum FGF23 level as a potential therapeutic target (29). However, an experimental study showed that administration of anti-FGF23 antibodies in uremic rats improved hyperparathyroidism, while aggravating vascular calcification and increasing mortality (30). The present study indicated that FGF23 exerts a protective effect overall, at least in patients with RRF. Therefore, further studies are needed to determine the total effect of a compensatory increase in the serum FGF23 level in patients undergoing PD with RRF.

Parathyroid hormone also exerts a phosphaturic effect by trafficking Na–Pi co-transporter type II to the apical membrane of the renal proximal tubules in healthy subjects and patients with mild to moderate CKD (31,32). However, in the present study, serum PTH level was associated with neither TmP/GFR nor total urinary Pi excretion. This finding is consistent with a previous study in hemodialysis patients (18). One possible explanation is the presence of PTH resistance in the renal proximal tubules, similar to that observed in bone of CKD patients. Although expression of PTH receptor 1 and its downstream signaling in patients undergoing PD with RRF has not been investigated, the PTH–PTH receptor-1/Na–Pi co-transporter type II axis is impaired under a low GFR state. Furthermore, serum whole PTH levels were relatively low in our study population. Considering the presence of PTH resistance in patients with low GFR, the low serum PTH levels may have accentuated the inability of PTH to excrete Pi into the urine.

The presence of FGFR and Na–Pi co-transporter type II in the peritoneal mesothelium has not been previously reported. These two molecules are indispensable for the phosphaturic actions of FGF23, thus, the absence of these molecules indicates the inability of FGF23 to excrete Pi actively into the peritoneal fluid. In this regard, the finding that the serum FGF23 level is not associated with peritoneal Pi excretion is conceivable. As shown in the present study, peritoneal Pi elimination was associated with the estimated Pi intake, peritoneal ultrafiltration volume, the D/P Cr ratio, and serum Pi level, which has been previously reported for some of these parameters (33,34). Collectively, Pi removal into the peritoneal fluid appears to be dependent on the complex diffusion mechanisms influenced by osmotic and electrochemical gradients, and not active excretion through the action of FGF23 (35–37).

We are aware of several limitations in the present study. First, the sample size was small. Second, the cross-sectional study design limited the ability to identify causal associations between urinary Pi regulation and circulating FGF23 level. Third, because urinary Pi excretion and TmP/GFR are also regulated by other factors that we did not measure, including estrogen and growth hormone, some unadjusted confounders may have affected the present analysis. Fourth, some patients used cinacalcet and vitamin D receptor activators. The use of these two drugs may have influenced the association found in this study, because these two drugs are known to affect serum FGF23 level (38,39). Although the use of both drugs was not associated with renal Pi elimination, these results might have been due to under-power. With all these limitations, we believe that the present data provide useful information for a better understanding of the association between Pi homeostasis and FGF23 in patients on PD.

CONCLUSION

Serum FGF23 level, but not parathyroid hormone level, is significantly associated with tubular maximal reabsorption of Pi normalized to glomerular filtration rate negatively and significantly associated with urinary Pi excretion positively in peritoneal dialysis patients, even after adjusting for potential confounders. The present study indicates the potential link between a highly elevated serum FGF23 level and Pi excretion in peritoneal dialysis patients with residual renal function. Further studies are thus needed to determine the threshold at which the benefits of increased circulating FGF23 exceed its harmful effects.

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Author contributions: SY, KT, and MT participated in the design, its coordination, and helped to draft the manuscript. SH, ST, ME, TN, and KM carried out the patient recruitment. HY and HO carried out the data acquisition and management. KT and TK performed the total management of the whole study. All the authors read and approved the final manuscript.

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AJKD
Original Investigation

Brain Atrophy in Peritoneal Dialysis and CKD Stages 3-5: A Cross-sectional and Longitudinal Study

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Background: Brain atrophy has been reported in patients with end-stage renal disease receiving hemodialysis, although its mechanism is unknown. However, little is known regarding brain atrophy in patients receiving peritoneal dialysis (PD). Therefore, we examined brain volume and its annual change over 2 years in PD patients compared with patients with non–dialysis-dependent chronic kidney disease (NDD-CKD).

Study Design: Cross-sectional and longitudinal cohort.

Setting & Participants: 62 PD patients and 69 patients with NDD-CKD with no history of cerebrovascular disease who underwent brain magnetic resonance imaging (MRI) were recruited in a cross-sectional study. Among them, 34 PD patients and 61 patients with NDD-CKD, who underwent a second brain MRI after 2 years, were recruited in a longitudinal study.

Predictor: PD therapy versus NDD-CKD.

Outcomes & Measurements: T1-weighted magnetic resonance images were analyzed. Total gray matter volume (GMV), total white matter volume (WMV), and cerebrospinal fluid space volume were segmented, and each volume was quantified using statistical parametric mapping software. Normalized GMV and WMV values were calculated by division of GMV and WMV by intracranial volume to adjust for variations in head size. We compared normalized GMV and normalized WMV between PD patients and patients with NDD-CKD in the cross-sectional study and the annual change in normalized GMV in the longitudinal study.

Results: In the cross-sectional study, normalized GMV, which was correlated inversely with age, was lower in PD patients than in patients with NDD-CKD. However, normalized WMV, which was not correlated with age, was comparable between the groups. Annual change in normalized GMV was significantly higher in PD patients than in patients with NDD-CKD. These differences remained significant even after adjustment for potential confounding factors.

Limitations: A short observation period and high dropout rate in the longitudinal study.

Conclusions: Decline in normalized GMV is faster in PD patients than in patients with NDD-CKD.

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INDEX WORDS: Chronic kidney disease (CKD); gray matter volume (GMV); white matter volume (WMV); magnetic resonance imaging (MRI); peritoneal dialysis (PD); brain atrophy; brain volume.

Cognitive impairment is common in individuals with chronic kidney disease (CKD), particularly those treated with dialysis.[1-4] CKD is known as an independent risk factor for cognitive impairment.[3] Because cognitive impairment is associated with brain atrophy in patients with diabetes,[5] ischemic brain injury,[6] and multiple sclerosis,[7] one possible mechanism of cognitive impairment in patients with CKD is brain atrophy. Rapid progression of brain atrophy has been reported in patients with end-stage renal disease (ESRD) treated by hemodialysis (HD) in previous studies, including ours.[8-12] Recent reports[13,14] have shown that brain atrophy is induced at an earlier phase of CKD and the severity of atrophy is associated with kidney function.

Taki et al[15] used a longitudinal design over 6 years in 381 healthy community-dwelling people to investigate the rate of age-related loss in global gray matter

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volume (GMV) and how sex and generational and cerebrovascular risk factors affected this rate. They calculated normalized GMV, which measures GMV as a percentage of total intracranial volume (corresponding to the sum of GMV, white matter volume [WMV], and cerebrospinal fluid [CSF] space volume) at baseline and follow-up by means of a fully automated technique. They showed that there were significant main effects of age, sex, and body mass index and an age-sex interaction on annual change in normalized GMV.

Although intradialytic hypotension may play a role in brain atrophy in patients with CKD receiving HD,[10] the cause of brain atrophy is unclear, and few data exist for brain volumes in patients treated by peritoneal dialysis (PD). However, a previous study by Kim et al[16] using cerebral magnetic resonance (MR) imaging (MRI) in PD patients reported a high prevalence of leukoaraiosis in the anterior circulation of the brain. This study also observed associations of old age, poorly controlled hypertension, and the PD procedure itself and/or ESRD with the presence of leukoaraiosis.

However, PD patients are more likely to be overhydrated and hypertensive than HD patients.[17-19] Considering the evidence that high blood pressure leads to a reduction in brain volume,[20] PD patients might show equivalent or more severe brain atrophy. Therefore, in the present study, we examined brain volume and its annual change in PD patients and compared them with those in patients with non–dialysis-dependent CKD (NDD-CKD; CKD stages 3-5) by cross-sectional and 2-year longitudinal studies.

METHODS

Participants

To investigate the degree of progression of cerebrovascular and cardiovascular complications in patients with NDD-CKD and HD and PD patients, we have conducted an observational study named the Observational Study on Cerebro- and Cardiovascular Complication in Non-Dialysis-Dependent, Hemodialysis, and Peritoneal Dialysis Patients With Chronic Kidney Disease (VCOHP) since December 2008. Inclusion criteria are as follows: (1) patients aged 20 to 80 years at the time of entry into the study, and (2) patients with NDD-CKD having estimated glomerular filtration rate < 60 mL/min/1.73 m^2 irrespective of urinalysis findings (CKD stages 3-5) or patients with ESRD receiving either HD or PD who initiated dialysis therapy within 2 years of study entry. Exclusion criteria are as follows: (1) pregnant women or women who have the possibility of pregnancy, (2) patients who previously have received another dialysis therapy for longer than 3 months, (3) patients who previously have undergone kidney transplantation, and (4) patients who have a history of brain injury, such as symptomatic stroke, traumatic brain injury, brain tumor, or a neuropsychiatric disease. Until July 2011, a total of 136 patients (1 HD patient, 64 PD patients, and 71 patients with NDD-CKD) were entered into the study. We eliminated 4 patients (2 PD patients and 2 patients with NDD-CKD) whose MR images at study entry were not available, and also eliminated 1 HD patient. The remaining 131 patients (62 PD patients and 69 patients with NDD-CKD) were recruited in a cross-sectional study.

Of the PD patients, 2 died (2 of brain hemorrhage, 1 each of acute myocardial infarction and hepatic cancer), 9 were transferred to HD therapy, 1 underwent kidney transplantation, 1 underwent permanent pacemaker implantation, 4 were transferred to another hospital, and 9 refused the second MRI examination. Of the patients with NDD-CKD, 1 died of gastric cancer, 1 underwent kidney transplantation, 3 were transferred to another hospital, and 3 refused the second MRI examination. Therefore, 95 patients (34 PD, 61 NDD-CKD) who underwent a second MRI after 2 years were included as longitudinal study participants (Fig 1). All patients provided informed consent. The Kyushu University Institutional Review Board approved all procedures (#23-112) and the

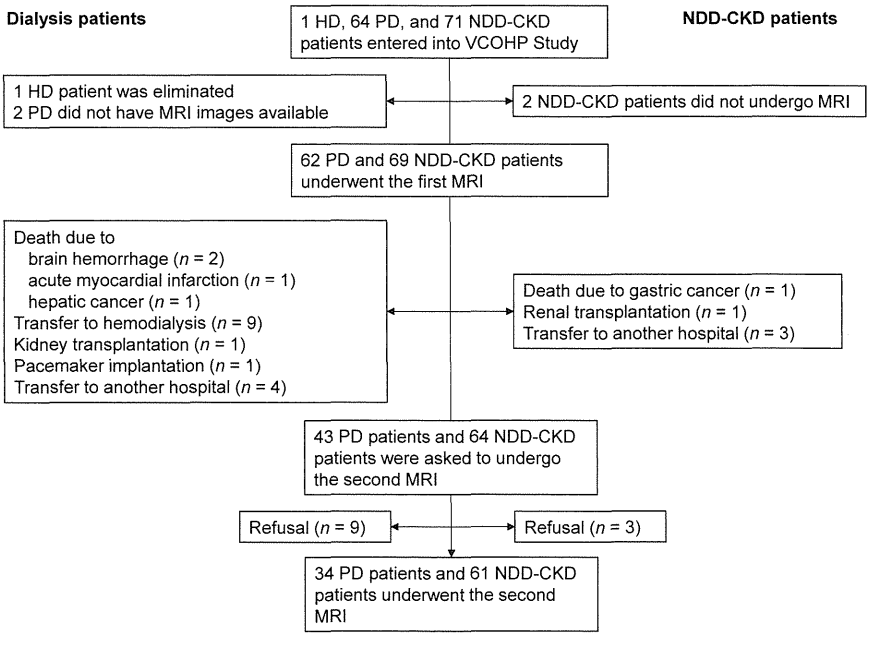

Figure 1. Flow diagram of participants. One hundred thirty-one (62 peritoneal dialysis [PD] and 69 non–dialysis-dependent chronic kidney disease [NDD-CKD]) patients were enrolled in the cross-sectional study. Of these, 36 (28 PD and 8 NDD-CKD) were excluded and the remaining 95 patients were enrolled in the longitudinal study. Abbreviations: HD, hemodialysis; MRI, magnetic resonance imaging; VCOHP, Observational Study on Cerebro- and Cardiovascular Complication in Non-Dialysis-Dependent, Hemodialysis, and Peritoneal Dialysis Patients With Chronic Kidney Disease.

study was registered in the UMIN clinical trial registry as the VCOHP Study (UMIN000001589).

Clinical Evaluation and Laboratory Measurements

All examinations were performed at the Medical Examination Center in Kyushu University Hospital. All patients underwent brain MRI. Clinical parameters were measured on the same day. Blood pressure in the brachial artery was measured in the sitting position after a 10-minute rest. Height and weight of participants were measured, and body mass index was calculated (kg/m^2).

Blood samples were collected on the same day as undergoing MRI and were analyzed at the laboratory of Kyushu University Hospital, except for whole parathyroid hormone and N-terminal pro–brain natriuretic peptide (NT-proBNP), which were analyzed at a commercial laboratory (SRL Inc, Fukuoka, Japan). Serum chemistry values were measured using an autoanalyzer with standard procedures (Hitachi 911 Auto Analyzer; Hitachi Co Ltd). Serum-corrected calcium levels were adjusted to serum albumin levels, according to Payne's formula, which is used commonly in patients with hypoalbuminemia. Hemoglobin A_{1c} values were measured by the National Glycohemoglobin Standardization Program method.[21]

Imaging Data

Brain MRI was performed for each participant using a 3.0-Tesla Philips Achieva magnetic resonance scanner (Philips Health Care) at Kyushu University Hospital. No major hardware upgrades occurred during the period. All patients underwent scanning with identical pulse sequences: 44 contiguous 3.0-mm thick axial planes of 3-dimensional T1-weighted images (magnetization-prepared rapid acquisition of gradient echo: echo time, 3.7 milliseconds; flip angle, 8; voxel size, 0.47 × 0.47 × 3 mm). MRI data were analyzed by a single investigator (H.Y.) who was blinded to the clinical information, as described previously.[15,22] We used Statistical Parametric Mapping 8 software (SPM8; Wellcome Department of Imaging Neuroscience, University College London) to preprocess brain images. The segmentation algorithm from SPM8 was applied to every T1-weighted MRI scan to extract tissue maps corresponding to gray matter, white matter, and CSF (Fig S1, available as online supplementary material).

We applied these processes using the MATLAB file "cg_vbm_optimized" (http://dbm.neuro.uni-jena.de/vbm.html). The voxel values of each segmented image did not consist of binary (ie, 0 or 1), but 256-level (ie, between 0/255 and 255/255) signal intensities, according to their tissue probability. The linear-normalized segmented images were restored to the native space using the inverse normalization parameters calculated in normalizing each MR image to the Talairach space to determine the volumes of each segment. Actual volumes of the entire normalized, segmented, and restored gray matter, white matter, and CSF space images were determined automatically by summing voxel volumes multiplied by each voxel value and dividing by 255.

To normalize for head size variability, normalized GMV and normalized WMV were calculated as percentage of total intracranial volume, calculated by adding GMV, WMV, and CSF space volume. Annual change in normalized GMV was calculated as (normalized GMV after 2 years − baseline normalized GMV) × 365/interval (days) between the first and second MRI. Moreover, to eliminate the effect of the baseline normalized GMV, we calculated annual percentage change in normalized GMV as (change in normalized GMV/baseline normalized GMV) × 365/interval (days) × 100.

Statistical Analyses

The *t* test, Mann-Whitney test, and χ^2 test were used as appropriate to describe the difference in patients' baseline characteristics. Multivariable-adjusted least square mean values of annual changes in normalized GMV were calculated using analysis of covariance. We performed univariable, age- and sex-adjusted, and multivariable regression analyses to confirm differences in normalized GMV between PD patients and patients with NDD-CKD. We entered age, sex, diabetes, history of cardiovascular disease, smoking habits, systolic blood pressure (SBP), hemoglobin level, baseline normalized GMV, and log-transformed NT-proBNP as covariates in the multivariable regression model by the forced entry method. We selected these covariates because they are considered to affect progression of brain atrophy. Then we performed a sensitivity analysis to alleviate the possible bias owing to a high dropout rate of the patients, especially those receiving PD, in the longitudinal study. We assumed that annual change in normalized GMV in the 36 excluded patients was stable at the same level as the general population, which was reported to be −0.20 percentage point per year in men and −0.24 percentage point per year in women by Taki et al.[23] Therefore, we applied these values to the annual change in normalized GMV in excluded participants in both PD patients and patients with NDD-CKD and performed regression analysis. All statistical analyses were performed using JMP, version 10.0, software (SAS Institute Inc).

RESULTS

Cross-sectional Study

Baseline characteristics and laboratory findings in the 131 patients are listed in Table 1. Age, sex, diastolic blood pressure, body mass index, and alcohol consumption were comparable between PD patients and patients with NDD-CKD. The prevalence of diabetes and smoking habits tended to be higher in PD patients than in patients with NDD-CKD, but this was not significant. SBP ($P = 0.005$) and levels of ferritin ($P = 0.003$), serum urea nitrogen ($P < 0.001$), serum creatinine ($P < 0.001$), serum phosphate ($P < 0.001$), β_2-microglobulin ($P < 0.001$), and whole parathyroid hormone ($P < 0.001$) were significantly higher, and hemoglobin ($P < 0.001$), total protein ($P < 0.001$), albumin ($P < 0.001$), total cholesterol ($P = 0.05$), and high-density lipoprotein cholesterol ($P = 0.001$) levels were significantly lower in PD patients than in patients with NDD-CKD. GMV and normalized GMV were associated negatively with age in patients with NDD-CKD and PD patients, whereas they were not associated with WMV and normalized WMV. Normalized GMV was significantly lower in PD patients than in patients with NDD-CKD at baseline (PD: 38.9% ± 2.7%; NDD-CKD: 40.9% ± 2.5%; $P < 0.001$), whereas normalized WMV was comparable (PD: 39.9% ± 1.5%; NDD-CKD: 40.1% ± 1.6%; $P = 0.4$; Fig 2A and B).

Longitudinal Study

Of 131 patients, 36 (28 PD and 8 NDD-CKD) patients were excluded and the remaining 95 patients were enrolled in the longitudinal study. Baseline characteristics and laboratory findings in the 95 included patients and 36 excluded patients are shown in Table 2. There were no differences in any variables between patients who were included and those who were excluded from the longitudinal study,

Table 1. Characteristics and Laboratory Data in the Cross-sectional Study

	PD (n = 62)	NDD-CKD (n = 69)	*P*
Age (y)	60 ± 12	61 ± 10	0.6
Male sex	41 (66)	37 (54)	0.2
Diabetes mellitus	24 (39)	16 (23)	0.06
Smoking habit	11 (18)	5 (7)	0.07
Alcohol consumption	32 (52)	35 (51)	0.9
Previous history of CVD	5 (8)	5 (7)	0.9
eGFR (mL/min/1.73 m^2)	NA	39.3 ± 12.4	NA
CKD stage			NA
Stage 3	NA	53 (77)	
Stage 4	NA	13 (19)	
Stage 5	NA	3 (4)	
Dialysis vintage (mo)	12 [6-17]	NA	NA
SBP (mm Hg)	143 ± 22	133 ± 15	0.01
DBP (mm Hg)	84 ± 14	82 ± 10	0.4
BMI (kg/m^2)	23.7 ± 3.0	23.9 ± 3.9	0.7
Laboratory data			
Hemoglobin (g/dL)	10.4 ± 1.1	12.6 ± 1.6	<0.001
Total protein (g/dL)	6.1 ± 0.5	6.8 ± 0.6	<0.001
Albumin (g/dL)	3.2 ± 0.4	3.9 ± 0.5	<0.001
SUN (mg/dL)	60 ± 15	26 ± 11	<0.001
Creatinine (mg/dL)	9.1 [7.0-11.2]	1.3 [1.1-1.8]	<0.001
CRP (mg/dL)	0.7 [0.2-2.5]	0.6 [0.3-1.2]	0.7
Total cholesterol (mg/dL)	177 [153-194]	185 [167-210]	0.05
Triglycerides (mg/dL)	128 [95-159]	139 [84-213]	0.4
HDL cholesterol (mg/dL)	44 [35-58]	54 [44-66]	0.001
LDL cholesterol (mg/dL)	100 ± 28	105 ± 29	0.4
Corrected Ca (mg/dL)	9.3 ± 0.6	9.3 ± 0.4	0.9
Phosphate (mg/dL)	4.8 ± 1.0	3.4 ± 0.6	<0.001
Ferritin (ng/mL)	119.5 [60.2-222.3]	71.8 [33.0-111.5]	0.003
β_2-Microglobulin (mg/L)	21.3 [17.2-26.3]	3.1 [2.4-4.5]	<0.001
Glycoalbumin (%)	14.1 ± 2.3	14.7 ± 2.2	0.1
Hemoglobin A_{1c} (%)	5.9 [5.5-6.2]	6.0 [5.7-6.2]	0.07
Whole PTH (pg/mL)	119 [55-222]	38 [27-56]	<0.001
NT-proBNP (pg/mL)	1,435 [646-3,148]	88 [42-183]	<0.001
Medications			
RAAS inhibitors	57 (92)	60 (87)	0.4
Ca antagonists	43 (69)	38 (55)	0.09
ESA	54 (87)	5 (7)	<0.001

Note: Values for categorical variables are given as number (percentage); values for continuous variables are given as mean ± standard deviation or median [interquartile range]. Conversion factors for units: creatinine in mg/dL to μmol/L, ×88.4; SUN in mg/dL to mmol/L, ×0.357; Ca in mg/dL to mmol/L, ×0.2495; cholesterol in mg/dL to mmol/L, ×0.02586; triglycerides in mg/dL to mmol/L, ×0.01129.

Abbreviations: BMI, body mass index; Ca, calcium; CKD, chronic kidney disease; CRP, C-reactive protein; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; ESA, erythropoiesis-stimulating agent; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NA, not applicable; NDD-CKD, non–dialysis-dependent chronic kidney disease; NT-proBNP, N-terminal probrain natriuretic peptide; PD, peritoneal dialysis; PTH; parathyroid hormone; RAAS, renin-angiotensin-aldosterone system; SBP, systolic blood pressure; SUN, serum urea nitrogen.

except for a significantly lower percentage of diabetes ($P = 0.03$) in patients with NDD-CKD and significantly higher levels of glycoalbumin ($P = 0.05$) and hemoglobin A_{1c} ($P = 0.04$) in PD patients in the excluded compared with included patients. In the 95 included patients, clinical characteristics and laboratory data at baseline were similar to those in the cross-sectional study among 131 patients, except for significantly lower levels of glycoalbumin ($P = 0.02$) and hemoglobin A_{1c} ($P = 0.003$) in PD patients compared with patients with NDD-CKD.

Normalized GMV after 2 years was significantly lower in PD patients than in patients with NDD-CKD irrespective of baseline normalized GMV (Fig 3). Annual change in normalized GMV was significantly higher in PD patients than in patients with NDD-CKD.

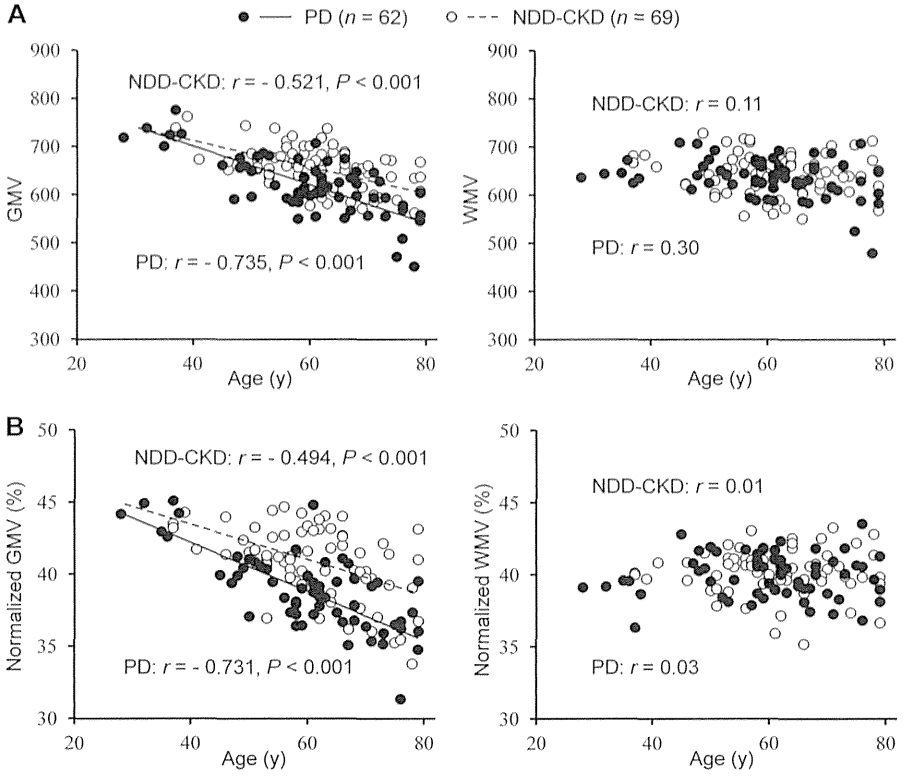

Figure 2. Inverse association of gray matter volume (GMV) and normalized GMV with age. (A) The association of GMV and white matter volume (WMV) with age in peritoneal dialysis (PD; closed circles; n = 62) and non–dialysis-dependent chronic kidney disease (NDD-CKD) patients (open circles; n = 69) are shown. (B) The association of normalized GMV and normalized WMV with age in PD (closed circles; n = 62) and NDD-CKD patients (open circles; n = 69) are shown. GMV and normalized GMV, but not WMV and normalized WMV, are associated inversely with age in PD and NDD-CKD patients.

This difference remained significant even after adjustment for various confounding factors, such as age, sex, diabetes, history of cardiovascular disease, smoking habits, SBP, hemoglobin concentration, baseline normalized GMV, and log-transformed NT-proBNP, by analysis of covariance (PD: -0.83 ± 0.14 percentage point/y; NDD-CKD: -0.38 ± 0.10 percentage point/y; $P = 0.004$; Fig 4) and multivariable regression analyses (Table 3).

In the sensitivity analysis, we also found that the difference between PD patients and patients with NDD-CKD remained significant, even after the final multivariable model (Table S1). This result confirmed the robustness of the difference in a faster decline in normalized GMV in PD patients than in patients with NDD-CKD.

Moreover, to eliminate the effect of the baseline normalized GMV, we performed multivariate regression analysis for the annual percentage change in normalized GMV, which was determined by the equation provided in the Methods section. We observed that this percentage change also was higher in PD patients than in patients with NDD-CKD, even after the final multivariable model (Table S2).

Finally, to determine the region with the most marked atrophy, we analyzed annual percentage change in normalized GMV by dividing the brain lobes into 4 categories: frontal lobe, parietal lobe, temporal lobe, and occipital lobe. A significantly faster decline in annual percentage change in normalized GMV was observed in PD patients than in patients with NDD-CKD in all regions, and this was especially remarkable in the parietal and temporal regions (Table S3).

DISCUSSION

The present study showed that a decline in normalized GMV was faster in PD patients than in patients with NDD-CKD, even after adjustment for potential confounding factors. Previous studies[8-11] have reported that brain atrophy progresses faster in patients with ESRD receiving HD than in controls. More recently, Drew et al[12] reported in a cross-sectional study that HD patients have a higher prevalence and severity of white matter disease, cerebral atrophy, and hippocampal atrophy compared with controls without kidney disease, even after adjusting for demographic factors, vascular risk factors, and

Table 2. Characteristics and Laboratory Data at Baseline in Included and Excluded Patients From the Longitudinal Study

	Included Patients			Excluded Patients	
	PD (n = 34)	NDD-CKD (n = 61)	*P*	PD (n = 28)	NDD-CKD (n = 8)
Age (y)	60 ± 11	61 ± 10	0.6	60 ± 13	62 ± 8
Male sex	21 (62)	32 (52)	0.4	20 (71)	5 (63)
Diabetes mellitus	10 (29)	16 (26)	0.7	14 (52)	0 (0)[a]
Smoking habit	6 (18)	5 (8)	0.2	5 (18)	0 (0)
Alcohol consumption	19 (56)	31 (51)	0.6	13 (46)	4 (5)
Previous history of CVD	2 (5.9)	4 (6.6)	0.9	3 (10.7)	1 (12.5)
eGFR (mL/min/1.73 m^2)	NA	38.7 ± 12.3	0.3	NA	43.5 ± 13.4
CKD stage			NA		
Stage 3	NA	46 (75)		NA	7 (88)
Stage 4	NA	12 (20)		NA	1 (13)
Stage 5	NA	3 (5)		NA	0 (0)
Normalized GMV (%)	39.1 ± 2.8	41.0 ± 2.5	<0.001	38.7 ± 2.6	40.1 ± 2.5
Dialysis vintage (mo)	12 [6-17]	NA	NA	12 [6-19]	NA
SBP (mm Hg)	141 ± 20	133 ± 15	0.04	145 ± 25	133 ± 17
DBP (mm Hg)	83 ± 14	81 ± 10	0.4	84 ± 14	86 ± 7
BMI (kg/m^2)	23.3 ± 3.0	23.8 ± 3.9	0.5	24.2 ± 3.1	24.8 ± 3.9
Laboratory data					
Hemoglobin (g/dL)	10.2 ± 1.1	12.6 ± 1.6	<0.001	10.5 ± 1.2	12.4 ± 2.0
Total protein (g/dL)	6.1 ± 0.5	6.8 ± 0.6	<0.001	6.1 ± 0.6	7.0 ± 0.6
Albumin (g/dL)	3.3 ± 0.4	3.9 ± 0.5	<0.001	3.2 ± 0.4	4.0 ± 0.6
SUN (mg/dL)	58 ± 13	26 ± 11	<0.001	61 ± 17	22 ± 10
Creatinine (mg/dL)	9.2 [7.5-10.5]	1.3 [1.1-1.8]	<0.001	8.6 [6.9-12.3]	1.3 [1.1-1.8]
CRP (mg/dL)	0.4 [0.2-2.2]	0.6 [0.3-1.1]	0.7	0.9 [0.3-2.9]	0.6 [0.3-1.1]
Total cholesterol (mg/dL)	178 [161-202]	183 [167-209]	0.4	177 [146-188]	194 [169-226]
Triglycerides (mg/dL)	134 [93-172]	129 [84-194]	0.8	120 [93-156]	226 [88-533]
HDL cholesterol (mg/dL)	49 [33-59]	54 [44-66]	0.04	42 [35-55]	50 [42-56]
LDL cholesterol (mg/dL)	102 ± 25	105 ± 28	0.6	99 ± 32	103 ± 37
Corrected Ca (mg/dL)	9.4 ± 0.6	9.3 ± 0.4	0.9	9.4 ± 0.6	9.5 ± 0.4
Phosphate (mg/dL)	4.8 ± 0.9	3.4 ± 0.6	<0.001	4.8 ± 1.0	3.3 ± 0.4
Ferritin (ng/mL)	110 [51-215]	77 [33-118]	0.04	125 [61-256]	63 [27-91]
β_2-Microglobulin (mg/L)	20.4 [17.0-25.7]	3.0 [2.5-4.5]	<0.001	23.0 [18.8-29.1]	3.5 [2.5-4.4]
Glycoalbumin (%)	13.6 ± 2.3	14.8 ± 2.3	0.02	14.7 ± 2.1[a]	14.3 ± 1.1
Hemoglobin A_{1c} (%)	5.7 [5.5-6.0]	6.0 [5.8-6.3]	0.003	6.0 [5.8-6.5][a]	6.0 [5.7-6.2]
Whole PTH (pg/mL)	115 [50-244]	37 [27-56]	<0.001	121 [70-219]	39 [27-57]
NT-proBNP (pg/mL)	1,015 [602-2,728]	88 [46-183]	<0.001	1,900 [913-4,385]	93 [25-431]
Medications					
RAAS inhibitors	33 (97)	54 (89)	0.1	24 (86)	6 (75)
Ca antagonists	22 (65)	35 (57)	0.5	21 (75)	3 (38)
ESA	29 (85)	5 (8)	<0.001	25 (89)	0 (0)

Note: Values for categorical variables are given as number (percentage); values for continuous variables are given as mean ± standard deviation or median [interquartile range]. Conversion factors for units: creatinine in mg/dL to μmol/L, ×88.4; SUN in mg/dL to mmol/L, ×0.357; Ca in mg/dL to mmol/L, ×0.2495; cholesterol in mg/dL to mmol/L, ×0.02586; triglycerides in mg/dL to mmol/L, ×0.01129.

Abbreviations: BMI, body mass index; Ca, calcium; CKD, chronic kidney disease; CRP, C-reactive protein; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; ESA, erythropoiesis-stimulating agent; GMV, gray matter volume; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NA, not applicable; NDD-CKD, non–dialysis-dependent chronic kidney disease; NT-proBNP, N-terminal probrain natriuretic peptide; PD, peritoneal dialysis; PTH; parathyroid hormone; RAAS, renin-angiotensin-aldosterone system; SBP, systolic blood pressure; SUN, serum urea nitrogen.

[a] $P < 0.05$ versus included patients.

prevalent vascular disease. However, to date, few data exist about brain atrophy in PD patients and there are no reports in only PD patients. Therefore, to our knowledge, the present study is the first detailed report of brain atrophy in these patients.

The mechanism of a faster decline in normalized GMV in PD patients is an area of great interest. We previously examined brain atrophy and lacunae using MRI. We found that brain atrophy, as determined by the ventricular to brain ratio, which was significantly

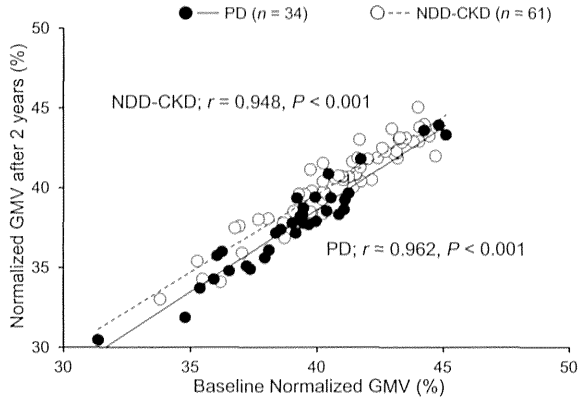

Figure 3. Association of normalized gray matter volume (GMV) at baseline and after 2 years in peritoneal dialysis (PD) and non–dialysis-dependent chronic kidney disease (NDD-CKD) patients. Normalized GMV after 2 years is significantly lower in PD than in NDD-CKD patients irrespective of baseline normalized GMV.

more severe in long-term HD patients than in age-matched controls, was associated with the severity of ischemic brain lesions.[8] We also reported that dialysis-related hypotension is among the contributing factors to progression of brain atrophy.[10] Based on these findings, potential brain ischemia is considered to cause brain atrophy.

Elevated blood pressure also is associated with lower cerebral blood flow and brain atrophy.[24-26] Of particular note is that 24-hour SBP has been revealed as an independent determinant for brain atrophy in healthy elderly people.[27,28] Moreover, sleep SBP, rather than 24-hour or awake SBP, and dipping of lesser magnitude in SBP and pulse pressure, are associated more significantly with brain atrophy.[28,29] These findings suggest involvement of salt-sensitive hypertension in brain atrophy because nocturnal hypertension is implicated in high sodium sensitivity and latent fluid retention.[30,31] Therefore, overhydration might affect brain atrophy. In our study, there was a significant difference in SBP and NT-proBNP levels between PD patients and patients with NDD-CKD at baseline, suggesting that hypertension and overhydration might contribute to the cause of brain atrophy in PD patients. However, in the present study, annual change in normalized GMV was greater in PD patients than in patients with NDD-CKD, even after adjustment for SBP and NT-proBNP level. Therefore, involvement of these factors in the faster decline in normalized GMV in PD patients appears unlikely.

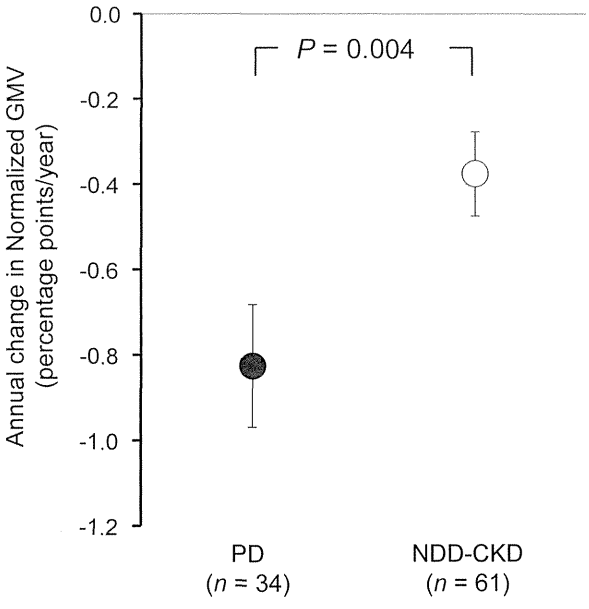

Figure 4. Comparison of annual change in normalized gray matter volume (GMV) between peritoneal dialysis (PD; closed circle) and non–dialysis-dependent chronic kidney disease (NDD-CKD; open circle) patients. Annual change in normalized GMV, as determined by subtraction of baseline normalized GMV from normalized GMV after 2 years, is significantly higher in PD patients than in NDD-CKD patients. Data are least square *mean* ± *standard error*.

In addition, other factors, such as some uremic toxins, oxidative stress, anemia, and depressed cerebral oxygenation, are considered to play a role in the rapid progression of brain atrophy in patients with ESRD. In this regard, we previously examined how anemia correction with recombinant human erythropoietin affects cerebral blood flow and oxygen metabolism in HD patients. We observed that cerebral oxygen metabolism was depressed irrespective of degree of anemia in HD patients.[32] Although cerebral oxygenation was not examined in PD patients in our previous study, depressed cerebral oxygenation might occur and contribute to rapid progression of brain atrophy in these patients because cerebral oxygenation was lower in HD patients than in controls and was intermediate in PD patients between HD patients and controls.[11]

To examine the possibility of involvement of other measurable values, such as serum urea nitrogen, serum creatinine, serum albumin, and serum phosphate, for the difference in change in normalized GMV between PD patients and patients with NDD-CKD, we added each value to the multivariable model described in Table 3. This difference was still significant and robust (data not shown). We speculate that the difference in change in normalized GMV between PD patients and patients with NDD-CKD is owed to some unmeasured factors, such as various uremic toxins, oxidative stress, or hemodynamic factors in the brain. Alternatively, PD therapy itself might contribute to a faster decline in normalized GMV.

A reduction in GMV is believed to reflect mainly degenerative changes in gray matter[33] because of shrinkage or loss of neurons.[34] Several neurodegenerative diseases, such as Alzheimer disease[35,36] and semantic dementia,[37] show less GMV compared with

Table 3. Univariable, Age- and Sex-Adjusted, and Multivariable-Adjusted Regression Analyses for Annual Change in Normalized GMV

	β (95% CI)	P
Univariable regression analysis: PD vs NDD-CKD	−0.476 (−0.647 to −0.304)	<0.001
Age- and sex-adjusted regression analysis		
PD vs NDD-CKD	−0.456 (−0.625 to −0.288)	<0.001
Age, per 10-y older	−0.004 (−0.081 to 0.073)	0.6
Men vs women	−0.213 (−0.378 to −0.047)	0.01
Multivariable regression analysis		
PD vs NDD-CKD	−0.450 (−0.736 to −0.164)	0.002
Age, per 10-y older	−0.034 (−0.131 to 0.062)	0.5
Men vs women	−0.240 (−0.424 to −0.055)	0.01
DM vs non-DM	−0.208 (−0.407 to −0.009)	0.04
Previous history of CVD vs no history	−0.229 (−0.577 to 0.120)	0.2
Smoker vs nonsmoker	−0.047 (−0.306 to 0.211)	0.7
SBP, per 10−mm Hg increase	−0.037 (−0.089 to 0.014)	0.2
Hemoglobin, per 1-g/dL increase	0.014 (−0.051 to 0.078)	0.7
Baseline normalized GMV, per 1% increase	−0.048 (−0.090 to −0.005)	0.03
Log-transformed NT-proBNP	−0.010 (−0.096 to 0.075)	0.8

Note: n = 95 for all analyses.

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; DM, diabetes mellitus; GMV, gray matter volume; NDD-CKD, non–dialysis-dependent chronic kidney disease; NT-proBNP, N-terminal probrain natriuretic peptide; PD, peritoneal dialysis; SBP, systolic blood pressure.

age-matched healthy older people. More recently, we demonstrated that uremia was associated with spatial working memory dysfunction because of neuronal cell damage by oxidative stress in CKD mice.[38] Furthermore, Zhang et al[39] recently showed that GMV was diffusely decreased in 57 patients with ESRD compared with healthy controls, and serum urea levels were associated negatively with changes in GMV in many regions. Based on these findings, we propose that uremic toxins might contribute to rapid brain atrophy in PD patients, probably through oxidative stress. In our recent report, treatment with the antioxidant agent TEMPOL (4-hydroxy-2,2,6,6-tetramethylpiperidin-1-oxyl) ameliorated cognitive impairment through inhibition of oxidative stress in CKD mice.[38] In addition, neuronal damage in CKD mice also was ameliorated by treatment with TEMPOL. We consider that uremia-induced neuronal damage could be prevented by treatment with an antioxidant, suggesting that brain atrophy can be prevented through inhibition of oxidative stress.

The strengths of the present study are as follows. First, this seemingly is the first detailed report on brain atrophy in PD patients. There are several reports on brain atrophy in HD patients and patients with NDD-CKD,[8-12] but almost no reports in only PD patients. Second, brain atrophy was determined more precisely and objectively using the SPM-based segmentation method compared with previous reports.[8-10,12] To our knowledge, including a recent report by Zhang et al,[39] only 2 cross-sectional studies[11,39] have been reported in which brain atrophy was evaluated using an SPM-based method in patients with ESRD. These studies showed that GMV was diffusely decreased in those patients, as shown in this study. Third, this was a longitudinal study performed for 2 years, in addition to a cross-sectional analysis. The cross-sectional and longitudinal studies showed a faster decline in normalized GMV with aging in PD patients compared with patients with NDD-CKD.

The present study has several limitations. First, the number of patients was fairly small. Second, the observation period of 2 years was short for evaluating changes in brain volume in the longitudinal study. We consider that these limitations might be alleviated partially by using the SPM-based method by which we precisely and objectively analyzed the MRI data. Third, normalized GMV was not evaluated in controls. Taki et al[15] estimated that the decline in normalized GMV might be faster in PD patients (-0.69 ± 0.41 percentage point/y) and similar in patients with NDD-CKD (-0.21 ± 0.40 percentage point/y) compared with healthy controls, according to a longitudinal study. They observed that the mean change in normalized GMV was −0.20 percentage point per year in men and −0.24 percentage point per year in women in the general population. Fourth, our results might have been biased by the exclusion of patients who did not undergo a second MRI after 2 years. However, we consider that the effect of this bias was negligible in this study because the characteristics, laboratory data, and baseline normalized GMV were comparable between PD patients and patients with NDD-CKD who were included and those who were excluded from the present study (Table 2). Additionally, no patients with NDD-CKD with diabetes were excluded, whereas a higher frequency of PD patients who were excluded had diabetes compared with those who were included. This finding suggests that the difference in annual change in normalized GMV between PD patients and patients with NDD-CKD would have been larger if none of the patients had been excluded from this study because diabetes is an independent risk factor for faster decline in normalized GMV, as shown in multivariable regression analysis (Table 3). Furthermore, sensitivity analysis did not change this result. Therefore, this bias is unlikely to have altered our findings.

In conclusion, a decline in normalized GMV was of significantly greater magnitude in PD patients than in patients with NDD-CKD independent of cardiovascular risk factors. Further studies are required to determine which patients receiving HD or PD have more severe brain atrophy and show more rapid progression, why progression is rapid in these patients, and how such a brain disorder can be prevented.

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Contributions: Research idea and study design: KT, HY; data acquisition: KT, HY, YK, TM, KM, MH, HK, KH; data analysis/interpretation: KT, HY, TY; statistical analysis: KT, HY, MN; supervision or mentorship: HH, TK. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. KT takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

SUPPLEMENTARY MATERIAL

Table S1: Univariable, age- and sex-adjusted, and multivariable-adjusted sensitivity regression analyses for annual change in normalized GMV.

Table S2: Univariable, age- and sex-adjusted, and multivariable-adjusted regression analyses for the annual percentage change in normalized GMV.

Table S3: Annual percentage change in normalized GMV according to brain regions.

Figure S1: Brain MR images.

Item S1: Explanation of corrections incorporated into the article in press.

Note: The supplementary material accompanying this article (http://dx.doi.org/10.1053/j.ajkd.2014.07.011) is available at www.ajkd.org

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RESEARCH ARTICLE

Dietary Patterns and Clinical Outcomes in Hemodialysis Patients in Japan: A Cohort Study

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Abstract

Background & Objectives

Little is known about actual dietary patterns and their associations with clinical outcomes in hemodialysis patients. We identified dietary patterns in hemodialysis patients in Japan and examined associations between dietary patterns and clinical outcomes.

Design, setting, participants, measurements

We used data from 3,080 general-population participants in the Hisayama study (year 2007), and data from 1,355 hemodialysis patients in the Japan Dialysis Outcomes and Practice Patterns Study (JDOPPS: years 2005–2007). Food intake was measured using a brief self-administered diet-history questionnaire (BDHQ). To identify food groups with the Hisayama population data, we used principal components analysis with Promax rotation. We adjusted the resulting food groups for total daily energy intake, and then we used those adjusted food-group scores to identify dietary patterns in the JDOPPS patients by cluster analysis (Ward's method). We then used Cox regression to examine the association between dietary patterns and a composite of adverse clinical outcomes: hospitalization due to cardiovascular disease or death due to any cause.

Results

We identified three food groups: meat, fish, and vegetables. Using those groups we then identified three dietary patterns: well-balanced, unbalanced, and other. After adjusting for potential confounders, we found an association between an unbalanced diet and important clinical events (hazard ratio 1.90, 95% C.I. 1.19–3.04).

Conclusions

Hemodialysis patients whose diet was unbalanced were more likely to have adverse clinical outcomes. Thus hemodialysis patients might benefit not only from portion control, but also from a diet that is well-balanced diet with regard to the food groups identified here as meat, fish, and vegetables.

Introduction

Dietary management is important to improve outcomes in hemodialysis patients. Clinical guidelines provide a recommended intake of micronutrients[1] to prevent hyperphosphatemia, hyperkalemia, hypertension, and water retention. Reduced intakes of protein, raw vegetables, and salt are recommended.[2–8] Excessive dietary restriction may of course result in malnutrition, but details of dietary patterns that might improve outcomes in hemodialysis patients are largely unknown.

Some previous research on nutritional epidemiology in kidney disease has focused on the absolute amounts of foods and micronutrients[7,9]. We focused instead on dietary patterns, which were identified by their balance (or unbalance) among food groups. Given that the prognosis of hemodialysis patients is better in Japan than in the US and Europe, we expected that an understanding of the relationship between dietary pattern and prognosis in hemodialysis patients in Japan would also provide useful information for hemodialysis care in other countries.

Here we report the results of a cohort study using data from hemodialysis patients participating in the Japan Dialysis Outcomes and Practice Patterns Study (JDOPPS) [10,11]. Our goals were to identify dietary patterns in those patients and to investigate relationships between dietary patterns and important clinical outcomes.

Methods

Ethics

The ethics committees of Kyushu University (Fukuoka, Japan) and Kyoto University (Kyoto, Japan) approved this study. Written informed consent was obtained from participants in the Hisayama study[12,13] and in the JDOPPS. The data were analyzed anonymously.

Participants and setting

The participants were selected from among Japanese volunteers participating in the Hisayama study[12,13] and Japanese hemodialysis patients participating in the JDOPPS.

The Hisayama study is a population-based study that has been conducted since 1961 in Hisayama-cho in the Kyushu region of Japan. Subjects are volunteers of various ages, and are considered to represent the age distribution of the population of Japan.[14,15] In the present study, we analyzed data from 3,080 people enrolled in the Hisayama study in 2007.

The JDOPPS is part of the International Dialysis Outcomes and Practice Patterns Study, an international longitudinal study of hemodialysis patients. Patients in the JDOPPS were selected randomly from among representative dialysis facilities in Japan, and they appear to represent all hemodialysis patients in Japan. The design of the DOPPS is detailed elsewhere.[16] After we excluded data from hemodialysis patients whose dietary intake was not measured and those with a daily energy intake of less than 500 kcal or more than 4,000 kcal, data from 1,355 hemodialysis patients who participated in the third phase of the JDOPPS between 2005 and 2007 were available for analysis.

The predictors

The methods regarding the predictors had four steps: (1) collection of data on food consumption, (2) identification of food groups, (3) computation of food-group scores, and (4) identification of dietary patterns. Those four steps are described in sequence below. We note that this method for identifying dietary patterns is based on foods and food groups, not on micronutrients, and that methods such as the one we used in this study are common in nutritional epidemiology.[17–20]

(1) Collection of data on food consumption (Hisayama study): Data on foods consumed were obtained using a brief self-administered diet-history questionnaire (the BDHQ).[21–23] The BDHQ is a 4-page structured questionnaire that contains questions about 58 foods and beverages, and allows the total energy intake and the intake of micronutrients to be estimated. Reports of previous studies indicate that food intake estimated using the BDHQ is consistent with intake measured using semi-weighted 16-day dietary records.[21,24] Food intake was measured with the BDHQ in the Hisayama study in 2007 and in the JDOPPS during the second year of JDOPPS enrollment, between 2006 and 2007.

(2) Identification of food groups (Hisayama study): To identify food groups, we conducted a principal components analysis (PCA). We used PCA with Promax rotation to reduce the results regarding the many foods listed in the BDHQ to a smaller set of food groups. That is, we used PCA to identify groups of foods that were eaten with approximately equal frequencies by the same people. We did those analyses with data from 3,080 participants in the Hisayama study. Here it is important to remember one similarity between PCA and other multivariate analyses: When the values of an independent variable are nearly the same among almost all participants, then that independent variable contributes little or no information to the results, and such variables should be deleted from the analyses. Therefore, in PCA it is common practice to delete items that vary by only small amounts between individuals [25], so for the PCA in this study we used 20 foods from the 58 in the BDHQ.

(3) Computation of food-group scores (Hisayama study and JDOPPS): After identifying food groups, we standardized the frequency of consumption of each food by using the mean and standard deviation in the Hisayama data. Then we used those standardized frequencies to compute food-group scores for each JDOPPS patient, and we used the residual method [26] to adjust those food-group scores for the total daily energy intake

(4) Identification of dietary patterns (JDOPPS): To identify dietary patterns in the JDOPPS patients, we used Ward's method of cluster analysis[27] on the energy-adjusted food-group scores. Thus, the patterns we identified were based on the relative amounts of foods from each food group that the JDOPPS patients actually ate.

The outcome

This study had one outcome, which was a composite of important adverse clinical events: hospitalization due to cardiovascular disease or death due to any cause. Cardiovascular disease included coronary heart disease, arrhythmia, congestive heart failure, cardiac valvular disease, cardiac myopathy, and pericarditis. The date and cause of hospitalization was ascertained approximately every 4 months in the JDOPPS.

Analyses (associations between dietary patterns and the outcome)

Cox regression analysis was used to investigate relationships between dietary patterns and the composite outcome. Those relationships were expressed as hazard ratios. The time between the second year of food-intake measurement using the BDHQ and the composite outcome was studied first. Two models were used. In Model 1, the covariates considered in estimating the hazard ratio were age, sex, and hemodialysis duration. In Model 2, the covariates were body mass index, serum albumin, total daily energy intake, and comorbid conditions (coronary artery disease, congestive heart failure, cerebrovascular disease, peripheral vascular disease, and diabetes).

In a sensitivity analysis, we adjusted for hemoglobin level, the dose of erythropoietin-stimulating agent (ESA), and Kt/V, in addition to the covariates included in Model 2. In another sensitivity analysis, we adjusted for smoking habit in addition to the covariates included in Model 2.

All analyses were done with SAS 9.2 (SAS Institute, Cary, NC) and STATA 13.1 software (STATA, College Station, TX).

Results

Population characteristics

Table 1 shows the characteristics of participants in the Hisayama study and in the JDOPPS. We included 3,080 participants from the Hisayama study. The mean of their ages was 62.7 years, and 10.6% of them had diabetes. We also included 1,355 hemodialysis patients from

Table 1. Demographic and clinical characteristics of the participants in the Hisayama study and in the JDOPPS.

	Hisayama(n = 3,080)	JDOPPS(n = 1,355)
Mean (SD) age, years	62.7 (12.0)	61.4 (11.9)
Male (%)	43.6	61.4
Mean (SD) dialysis duration, years	NA	7.6 (7.2)
Mean (SD) BMI	23.1 (3.5)	21.1 (3.2)
Comorbid conditions (%)		
Diabetes	10.6	32.1
Coronary heart disease	6.0	41.3
Cerebrovascular disease	3.7	11.5
Other cardiovascular disease	8.2	30.6
Peripheral vascular disease	0.2	15.9
Cancer	7.5	9.4
Mean (SD) albumin, g/dL	4.2 (0.3)	3.8 (0.4)

JDOPPS: Japan Dialysis Outcomes and Practice Patterns Study, NA: not applicable, BMI: body mass index.

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the JDOPPS. The mean of their ages was 61.4 years, and 32.1% of them had diabetes. The mean duration of their dialysis was 7.6 years. The proportions of comorbidities, including diabetes and cardiovascular disease, were higher in the JDOPPS group than in the Hisayama group.

Food groups (general–population results)

In the first PCA, "natto (fermented soybean)" had a moderate loading on 2 components. We therefore deleted "natto" and ran the PCA again. The first three components had eigenvalues greater than 1: 5.69, 1.53, and 1.35, which accounted for 28.4%, 7.8%, and 6.74% of the variance, respectively. As shown in Table 2, three food groups were identified. The first group included carrot & pumpkin, root vegetables, cabbage (cooked), mushrooms, seaweed, lettuce & cabbage (raw), potatoes, tofu (bean curd) & fried tofu, turnip (radish), and tomato. This we call the vegetables group. The second group included squid & octopus & shrimp & shellfish, dried fish, fatty fish, lean fish, and small fish with bones. This we call the fish group. The third group included ham, pork & beef, chicken, and eggs. This we call the meat group.

Table 2. Coefficients after Promax rotation (Principal Components Analysis, Hisayama data).

		Component		
Food Item		**1**	**2**	**3**
Carrot/pumpkin		0.798	−0.079	0.001
Root vegetables		0.754	−0.055	−0.022
Green leafy vegetables		0.705	−0.092	0.067
Cabbage (cooked)		0.686	−0.146	0.148
Mushrooms		0.636	0.058	0.013
Seaweed		0.591	0.135	−0.127
Lettuce/cabbage (raw)		0.543	−0.122	0.260
Potatoes		0.530	0.168	−0.057
Tofu (bean curd)/fried tofu		0.504	0.154	−0.026
Turnip (radish)		0.497	0.189	−0.106
Tomato		0.426	0.104	−0.003
Dried fish		−0.081	0.693	0.087
Fatty fish		0.027	0.630	0.116
Lean fish		0.103	0.594	−0.034
Small fish with bones		0.160	0.591	−0.179
Squid, octopus, shrimp, shellfish		−0.095	0.536	0.248
Ham		−0.135	0.042	0.718
Pork/beef		0.054	0.019	0.715
Chicken		0.057	0.121	0.564
Eggs		0.116	−0.012	0.474
Coefficents of correlation	1	1.000	0.430	0.267
	2		1.000	0.242
	3			1.000
Deleted food				
Natto				

Data on 20 foods were analyzed with principal components analysis (Promax rotation). The first three components had eigenvalues greater than 1: 5.69, 1.53, and 1.35, which accounted for 28.4%, 7.8%, and 6.74% of the variance.

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