Chronic Kidney Disease and Subclinical Brain Infarction Increase the Risk of Vascular Cognitive Impairment: The Sefuri Study

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Background and Purpose: The purpose of this study was to determine the complex associations among chronic kidney disease (CKD), subclinical brain infarction (SBI), and cognitive impairment. *Methods:* We used structural equation modeling (SEM) to examine the complex relationships among CKD, SBI, and cognitive function with Mini-Mental State Examination (MMSE; global function) and modified Stroop test (executive function) in a population-based cohort of 560 non-demented elderly subjects. *Results:* Path analysis based on SEM revealed that the direct paths from estimated glomerular filtration rate (eGFR) to SBI and from SBI to executive function were significant ($\beta = -.10$, $P = .027$, and $\beta = .16$, $P < .001$, respectively). Furthermore, the direct path from eGFR to executive function was also significant ($\beta = -.12$, $P = .006$), indicating that the effects of CKD on executive function are independent of SBI. The direct paths from age and education to global cognitive function were highly significant ($\beta = -.17$ and .22, respectively, $P < .001$), whereas the direct path from eGFR to MMSE was not significant. *Conclusions:* Our findings indicate that CKD confers a risk of vascular cognitive impairment or executive dysfunction through mechanisms dependent and independent of SBI. Treating CKD may be a potential strategy to protect against vascular cognitive impairment or executive dysfunction in healthy elderly subjects. **Key Words:** Small vessel disease—glomerular filtration rate—vascular cognitive impairment—magnetic resonance imaging—silent stroke—executive function.
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Introduction

Chronic kidney disease (CKD) is a significant and independent risk factor in the development of cognitive dysfunction; cognitive function was found to be reduced even in community-based subjects, with only moderate reductions in estimated glomerular filtration rate (eGFR) (Supplementary Table S1).[1-11] In several studies, an association was found between CKD and cognitive impairment, particularly after tests assessing executive cognitive function, after adjustment for several potential confounders.[2,3,6,10] The predominant impairment of executive function in CKD resembles that in stroke (i.e., vascular cognitive impairment).[12] In contrast, other studies have shown that kidney function is inversely related to episodic or delayed memory in addition to executive function; episodic memory is often the earliest sign of Alzheimer disease rather than

cerebrovascular disease.[4,5] Individuals with CKD had a greater volume of white matter lesions (WMLs) and an increased prevalence of subclinical brain infarction (SBI) on magnetic resonance imaging (MRI).[13] CKD may cause cognitive impairment indirectly through cerebrovascular lesions, because CKD or low eGFR was most strongly associated with SBI of the cerebral small vessel disease subtype.[14,15]

However, several studies, including ours, have shown that SBI and CKD are independently associated with cognitive dysfunction or dementia incidence after adjusting for potential confounders.[16-19] Previously, we reported that CKD was associated with SBI, and CKD and SBI were independently associated with frontal lobe (executive) dysfunction.[14,16] Nonetheless, the relationships among CKD, SBI, and cognitive function examined with "first-generation" multivariate regression-based analysis have not been elucidated completely, as the postulation of a simple model structure (i.e., one dependent and several independent variables) may be too limiting for an analysis of more complicated and more realistic situations (multiple dependent and independent constructs).[20] Our previous study with "next-generation" structural equation modeling (SEM) demonstrated a distinct correlation between vascular depression or apathy and leisure-time physical inactivity beyond the limitation of the simple model structure.[21] In the current study, we investigated the relationships among CKD, SBI, and cognitive function by further extending the study period, and through SEM to overcome the limitations of first-generation statistical techniques.

Subjects and Methods

Study Design and Participants

This is a cross-sectional observational investigation on community-dwelling elderly people.

Between 1997 and 2015, we examined 828 volunteers aged ≥40 years living in the rural community of Sefuri village, Saga, Japan. These subjects were living independently without apparent dementia. We excluded 165 subjects aged <59 years; these subjects principally did not undergo tests for cognitive function. We also excluded 33 subjects who did not undergo the Mini-Mental State Examination (MMSE); in 2014, MMSE was not performed. In total, 70 subjects were excluded because of a history of stroke (n = 26); psychiatric disorders, including depression (n = 18); claustrophobia or contraindications to MRI (n = 9); brain tumor (n = 3); a history of head trauma (n = 3); chronic subdural hematoma (n = 1); malignant neoplasm (n = 1); renal transplantation (n = 2); and insufficient clinical information (n = 7). Finally, we analyzed 560 subjects in the present study.

The National Hospital Organization Hizen Psychiatric Center Institutional Review Board approved the study (approval number: 24-4), and written informed consent was obtained from all participants.

Definition of Vascular Risk Factors

Vascular risk factors were defined as described previously.[14] Briefly, arterial hypertension was defined as a history of repeated blood pressure recordings ≥140/90 mm Hg or the subject was being treated for hypertension. Diabetes mellitus was defined as fasting plasma glucose ≥7.77 mmol/L or HbA1c ≥6.5%, or a previous diagnosis of diabetes mellitus. Hyperlipidemia was defined as total serum cholesterol concentration ≥5.69 mmol/L or if the subject was being treated for hyperlipidemia.

Serum creatinine values, measured by the enzymatic method, were used for the Japanese modification of eGFR from the Modification of Diet in Renal Disease Study equation: eGFR (mL/min/1.73 m^2) = 194 × (serum creatinine [mg/dL])$^{-1.094}$ × (age)$^{-0.287}$ × (.739 if female).[22] CKD was defined as <60 mL/min/1.73 m^2 according to the standard guideline.[23]

Assessment of Cognitive Function

All participants underwent a structured clinical interview. All subjects completed MMSE for global function assessment and modified Stroop test for executive or frontal lobe function assessment.[16,24] The modified Stroop test comprised two parts; subjects were asked to name the colors of dots in Part I and colors of incongruent words (Chinese characters) in Part II. The difference in time between the two parts was considered to be due to interference effects, and the subject was considered to have executive dysfunction if the total score was above the most prolonged fifth quintile (i.e., ≥33 seconds in the present study). The subject was judged as having global cognitive dysfunction if the total score of MMSE was below the lowest fifth quintile (i.e., <25 points).

Assessment of MRI Findings

The combination of T1-weighted, T2-weighted, and fluid attenuated inversion recovery images is required to accurately detect both SBI and WMLs.[25] The definitions and imaging methods were concurrent with the neuroimaging standards for studies on small vessel disease.[26] SBI was defined by low signal intensities on T1-weighted images, and their size was 3 mm or larger as described previously[14,16]; we differentiated enlarged perivascular spaces from SBI based on their location, shape, and size. In the SEM analysis, SBI was defined as 0, no infarct (n = 462); 1, 1 infarct (n = 57); 2, 2 infarcts (n = 21); and 3, ≥3 infarcts (n = 20). WMLs were defined as isointense with normal brain parenchyma on T1-weighted images, and high signal intensity areas on T2-weighted images, and were classified as deep white matter lesions (DWMLs) and periventricular hyperintensities (PVHs).[27] All scans were reviewed independently by two authors (H.Y. and A.U.) who were blinded to all clinical data.

Statistical Analysis

All clinical variables are presented as mean ± standard deviation. A significant level of .05 was used for statistical significance. Multivariate analysis was done using the forward stepwise method of logistic regression analysis. We investigated the relationships among SBI, eGFR, and cognitive impairment using SEM with the IBM SPSS Amos version 22.0 (SPSS Japan Inc., Tokyo, Japan). We examined several indices of model fit for SEM analysis with their acceptable thresholds: low chi-square values relative to degrees of freedom with an insignificant P value ($P > .05$); values >.95 for goodness-of-fit index, adjusted goodness-of-fit index, and comparative fit index; and values <.07 for root mean square error of approximation.

Results

The subjects comprised 221 men and 339 women with a mean age of 72.1 years (Table 1). The prevalence of hypertension, diabetes mellitus, and hyperlipidemia was 43.8%, 5.0%, and 20.7%, respectively. The mean value of eGFR was 72.2 ± 16.0 mL/min/1.73 m^2, and the frequency of CKD was 19.6%. SBI, DWMLs, and PVHs were detected in 98 (17.5%), 246 (43.9%), and 158 (28.2%) of the 560 participants, respectively.

In the preliminary analysis with the forward stepwise logistic regression analysis, the independent predictors of executive dysfunction (fifth quintile) were age, SBI, and eGFR or CKD, whereas DWMLs and PVHs failed to enter into the equation (Supplementary Table S2). Furthermore, milder renal dysfunction (eGFR <75 mL/min/1.73 m^2) than

Table 1. *Characteristics of the study population*

Characteristic	Value (n = 560)
Age, mean (SD), years	72.1 (7.7)
Male sex, n (%)	221 (39.5)
Education, mean (SD), years	9.8 (2.4)
Mini-Mental State Examination, mean (SD)	26.7 (2.9)
Body mass index, mean (SD), kg/m^2	22.9 (3.4)
Hypertension, n (%)	245 (43.8)
Systolic BP, mean (SD), mm Hg	143.4 (22.1)
Diastolic BP, mean (SD), mm Hg	78.1 (10.7)
Diabetes mellitus, n (%)	28 (5.0)
Hyperlipidemia, n (%)	116 (20.7)
Alcohol, n (%)	171 (30.5)
Smoking, n (%)	66 (11.8)
Chronic kidney disease, n (%)	110 (19.6)
eGFR, mean (SD), mL/min/1.73 m^2	72.2 (16.0)
Subclinical brain infarction, n (%)	98 (17.5)
Deep white matter lesions, n (%)	246 (43.9)
Periventricular hyperintensities, n (%)	158 (28.2)

Abbreviations: BP, blood pressure; eGFR, estimated glomerular filtration rate; SD, standard deviation.

CKD was also associated with executive dysfunction (Supplementary Table S2, model 3).

Path analysis based on SEM indicated that the direct paths from eGFR and SBI to executive function—indicated as "Stroop" in Figure 1—were significant ($\beta = -.12$, $P < .01$, and $\beta = .16$, $P < .001$, respectively). Furthermore, the direct path from eGFR to SBI was significant ($\beta = -.10$, $P < .05$). The direct paths from age and education to global cognitive function (MMSE) were highly significant ($\beta = -.17$ and .22, respectively, $P < .001$), whereas the direct path from eGFR to MMSE was not significant. The measures of model fitness were as follows: relative chi-square value = 1.83, goodness-of-fit index = .995, adjusted goodness-of-fit index = .977, comparative fit index = .991, and root mean square error of approximation = .038. Thus, the presented model reasonably fit the data.

Discussion

The present SEM results showed that CKD was associated with executive dysfunction in healthy elderly subjects through pathways dependent and independent of SBI in healthy elderly subjects. The cognitive impairment associated with CKD was predominant in executive function rather than global cognition. Similar results were shown by Umemura et al, who revealed that albuminuria and low eGFR were associated with frontal lobe dysfunction independent of cerebral small vessel disease in patients with type 2 diabetes.[19] Furthermore, Seliger et al reported that moderate renal impairment, reflected by a higher serum creatinine level, was associated with an increased risk of incident vascular dementia but not Alzheimer-type dementia.[17] Therefore, the present results may support the vascular hypothesis of CKD-related cognitive dysfunction, although the extent of ischemic pathology did not correlate well with severity or pattern of neuropsychological impairments, thus challenging the utility of SBI-independent executive dysfunction as a diagnostic marker for vascular cognitive impairment.[28]

There are several biologically plausible mechanisms through which CKD could result in cognitive dysfunction.[12] CKD and silent or subclinical brain ischemic lesions share many common risk factors; juxtamedullary afferent arterioles in the kidney and perforating arterioles in the brain arise directly from large high-pressure arteries, which predispose both organs to hypertensive vascular damage (i.e., strain vessel hypothesis).[29] Nonetheless, CKD increases the risk of SBI or WMLs independent of classical vascular risk factors.[14,30] In contrast, Miwa et al found that predominantly mild CKD was associated with Alzheimer-type dementia, whereas moderate-to-severe CKD showed a positive association with vascular dementia.[18] In this context, Tsuruya et al showed that frontal and temporal gray matter atrophy could be an independent risk factor for executive function in patients with CKD stages 3-5.[31]
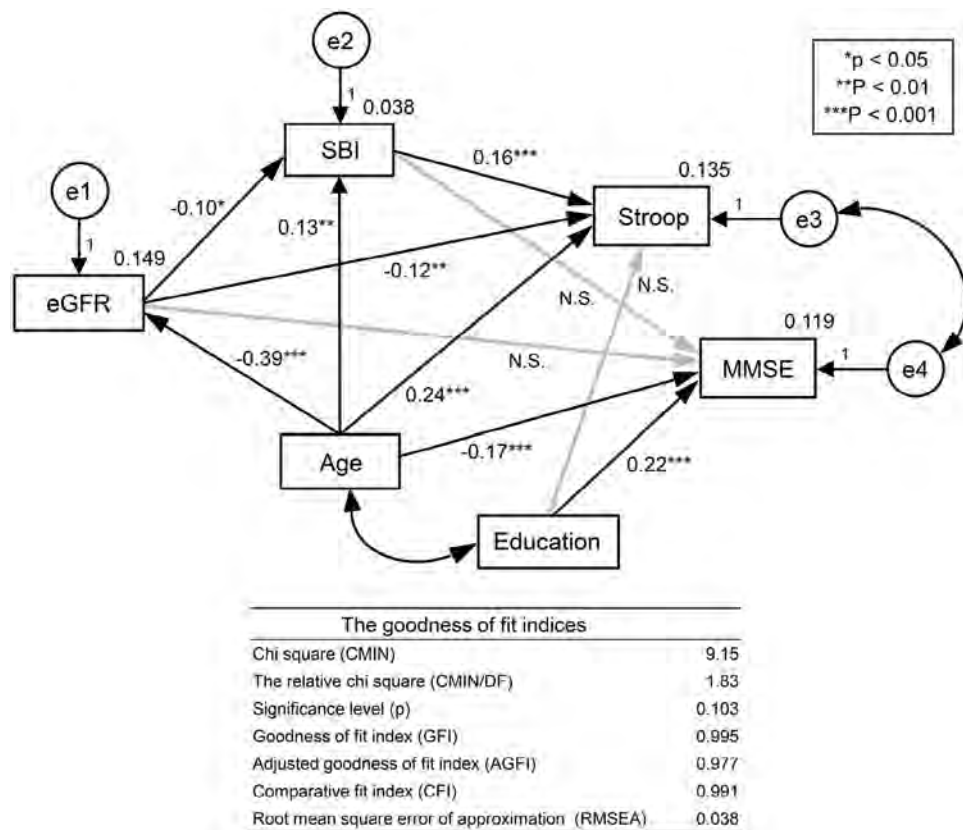
Figure 1. *Structural equation modeling (SEM) of renal function, subclinical brain infarction, and cognitive function. The SEM is described as path diagrams, where the squares represent measured observations and circles represent latent constructs. Single-headed arrows represent simple regression relationships, and double-headed arrows represent correlations. The direct paths from estimated glomerular filtration rate (eGFR) to subclinical brain infarction (SBI) and from SBI to executive function (Stroop) were significant. Further, the direct path from eGFR to executive function was significant, indicating effects of chronic kidney disease on executive function independent of SBI. Abbreviations: MMSE, Mini-Mental State Examination; N.S., not significant.*

Another possible explanation for the relationship between CKD and cognitive dysfunction—not through "typical" SBI—would be that lesions that are not readily detectable by conventional MRI, such as microinfarcts and tissue changes in the white matter appearing normal on MRI, played an important role as major determinants of cognitive impairment.[32,33]

Our study is based on a cross-sectional study design that limits the interpretation of the results with respect to cause and effect; in particular, CKD may be the cause of subsequent cognitive decline. Another limitation is that only modified Stroop test and MMSE were performed (i.e., narrow scope of the cognitive assessment). Strengths of our study include the relatively large number of community-dwelling subjects, the use of MRI, and the adopted alternative statistical tool (i.e., SEM)—in addition to the first-generation regression-based approaches—to investigate concurrent relationships among multiple constructs such as CKD, SBI, and cognitive function.

In conclusion, treating CKD may be a potential strategy to protect against executive dysfunction or vascular cognitive impairment in healthy elderly subjects.

Appendix: Supplementary Material

Supplementary data to this article can be found online at doi:10.1016/j.jstrokecerebrovasdis.2016.10.002.

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