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Kidney dysfunction and silent brain infarction in generally healthy adults

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ABSTRACT

Background: The association between silent brain infarction (SBI) and estimated glomerular filtration rate (eGFR)-based kidney dysfunction has not yet been definitively confirmed. This study aimed to investigate the association in generally healthy adults without a previous history of stroke or overt kidney disease.
Methods: The data from the screening health check-up program in the Seoul National University Hospital Health Promotion Center from January 1, 2009 to December 31, 2013 were used. A total of 2594 subjects who underwent brain MRI as part of health screening were included. SBIs were identified using T2-weighted and FLAIR images. Kidney dysfunction was defined as eGFR < 60 ml/min/1.73 m^2. To assess the effect of kidney dysfunction on the small perforating branches of cerebral vessels, subgroup analysis was performed using the presence of SLI as a dependent variable.
Results: The mean age was 56.8 ± 9.3 years, and 1422 subjects (54.8%) were male. The mean eGFR level was 81.9 ± 15.4 ml/min/1.73 m^2. The prevalence rates of kidney dysfunction and SBI were 5.1% and 7.1%, respectively. A higher proportion of subjects with SBI had kidney dysfunction than subjects without SBI (14.6% vs. 4.4%). The number of SBI lesions tended to increase with the progression of kidney dysfunction (p for trend < 0.001). In multivariate logistic regression analyses, kidney dysfunction was significantly associated with the presence of SBI (adjusted odd ratio = 1.99 to 2.21 in all four models). The same significant association was consistently identified in subgroup analyses using silent lacunar infarction (adjusted odd ratio = 1.71 to 1.87 in all four models).
Conclusion: Kidney dysfunction was found to be an independent risk factor for the presence and number of SBI in generally healthy adults. Physicians treating patients with a decreased creatinine-based eGFR level should try to identify and modify the coexisting risk factors of stroke followed by SBI.

1. Introduction

Silent brain infarction (SBI) is a cerebral infarction that is identified on a brain imaging study, and that does not cause clinical symptoms or signs of localized or global loss of brain functions [1]. Advances in imaging technology have enabled identification of various tiny brain lesions, including SBIs, by using brain magnetic resonance imaging (MRI) [2]. SBIs are related to many neurological symptoms and signs such as visual field defect and disturbances in the extremities [3,4]. Especially for elderly patients, the presence of SBI increases the risk of physical functional impairment, cognitive impairment, and dementia [5,6]. Furthermore, SBI is known to be a strongly predictive factor for future clinically overt stroke [7]. In the general population, the presence of SBI increases the risk for subsequent cerebrovascular events by two to four times [5,8].

Previous studies have suggested many risk factors for SBIs [7]. In particular, many researchers have focused on the possible role of kidney dysfunction in SBI as the kidney has similar microvascular beds to those seen in the brain [9]. Although various markers of kidney function

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have been used in previous studies [4,10–16], the gold standard for the evaluation of kidney function is the creatinine-based eGFR level [17,18]. However, the association between kidney dysfunction from creatinine-based eGFR level and SBI has not been consistent across studies [7]. Furthermore, the results from specific disease groups, including patients with chronic kidney disease [10,12,13,15], diabetes [11], or hypertension [16], cannot guarantee the generalizability of the extant results. Above all, the discordant results from general population level studies have raised controversy regarding the association between eGFR-based kidney dysfunction and SBI [19–24]. In contrast to the studies in Western populations [23,24], the association has been consistently significant in East Asian populations, including in Japan and Taiwan [19–22]. Although this finding supports the assumption that Asian populations with kidney dysfunction are more likely to have SBI, it is not a definitive association due to possible biases ranging from the included age group (only patients aged 61 and 72 years) [20], SBI prevalence (28.4%) that is too high to represent the general population [21], small number of subjects with SBI ($n = 62$) [22], or lack of consideration for multiple co-factors [19].

This study aimed to investigate the association between eGFR-based kidney dysfunction and SBI in generally healthy Korean adults.

2. Methods

2.1. Study population and clinical variables

The data from the screening health check-up program in the Seoul National University Hospital Health Promotion Center from January 1, 2009 to December 31, 2013 were used. The health check-up program included a detailed questionnaire about the subject's sociodemographic profiles, lifestyle, and previous/present medical histories. In addition, a trained family physician checked each subject's past medical histories, current medications, and performed any necessary physical and neurological examination. In essence, the program consisted of anthropometric and blood pressure measurements, blood tests, urine tests, and basic cancer screening. Optionally, subjects could undergo brain MRI at their own expense.

A total of 2699 subjects aged 30 or older underwent brain MRI during the study period. Among them, 46 subjects were excluded since their serum creatinine, low density lipoprotein cholesterol (LDL), high density lipoprotein (HDL) cholesterol, or hemoglobin A1c levels were missing. Finally, after excluding 59 subjects with a previous history of stroke, a total of 2594 subjects were included.

This study was approved by the institutional review board at Seoul National University Hospital. (IRB No. 1502-026-647).

2.2. Clinical variables

All examinations were performed after overnight fasting. The subjects' weight and height were measured while wearing a light gown. Body mass index was calculated as weight (kg) divided by height^2 (m^2). After resting for >5 min in a sitting position, the blood pressure was measured. Blood tests for metabolic and lipid profiles, including serum fasting glucose, hemoglobin A1c, triglyceride, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, total cholesterol, and creatinine level, were performed. To identify the prevalence of hypertension, diabetes mellitus, and dyslipidemia, we categorized subjects as follows: hypertension (taking drugs for hypertension or when systolic blood pressure ≥ 140 mm Hg, or when diastolic blood pressure ≥ 90 mm Hg; diabetes mellitus (taking drugs for diabetes mellitus or had a fasting blood glucose level ≥ 126 mg/dl or an HbA1c ≥ 6.5%; dyslipidemia (taking drugs for dyslipidemia or when their total cholesterol level was ≥240 mg/dl).

The eGFR, which was calculated from the Modification of Diet in Renal Disease (MDRD) eq. ($175 \times \text{serum creatinine}^{-1.154} \times \text{age}^{-0.203} \times 0.742$ [for females]), was used as a marker of kidney function [17].

We divided smoking habits into two categories: 1) non- or former smokers, and 2) current smokers. In addition, subjects taking anti-platelet drugs or anti-coagulants (such as aspirin, clopidogrel, or warfarin) were identified.

2.3. MRI protocol and definition of SBI

Brain MRI was performed at a field strength of 1.5 T (Signa, GE Healthcare, Milwaukee, WI or Magnetom SONATA, Siemens, Munich, Germany). The detailed description of the MRI protocol of the present study is provided elsewhere [25]. All images were reviewed by two board-certified neurologists (J-S Lim and H-M Kwon), who were blinded to the subjects' clinical information. Disagreements were settled after discussion with a third board-certified neurologist.

An SBI was defined as a focal infarction sized 3 mm or more in diameter with a high intensity signal in T2-weighted FLAIR images and a low intensity signal in T1-weighted images within the whole brain. For the subgroup analysis, silent lacunar infarction (SLI) was defined as a focal infarction with a fluid-filled cavity (signal similar to the cerebrospinal fluid signal) 3 mm to 15 mm in diameter within subcortical regions [26].

2.4. Statistical analysis

At first, univariate analysis (*t*-test and chi-square test as appropriate) according to the presence of SBI was performed for the baseline characteristics. The *p*-value was estimated to assess the dose-response relationship between the number of SBI lesions and the stage of renal function as defined by the US National Kidney Foundation [27].

To assess the association between kidney dysfunction and the presence of SBI, multivariate logistic regression analysis was performed. Covariates were selected from items of the health check-up program considering possible risk factors identified in previous studies [7]. Four individual models were included in the multivariate analysis: 1) model 1 adjusted for demographic variables; 2) model 2 adjusted for the variables in model 1 and additional variables for lifestyle and current medications; 3) model 3 adjusted for the variables in model 1 and additional variables for anthropometric, metabolic, and lipid profiles; and 4) model 4 adjusted for the all variables in models 1, 2, and 3.

As the MDRD equation is not reliable in subjects with eGFR ≥ 60 ml/min/1.73 m^2 [28,29], the Kidney Disease Improving Global Outcomes (KDIGO) recommended reporting higher values of eGFR as ≥60 [30]. Therefore, we categorized those with eGFR ≥ 60 as a single reference group for the multivariate analysis. In addition, as the number of subjects with eGFR < 30 was too small ($n = 1$ for subjects without SBI and $n = 4$ for subjects with SBI), we used a single category of eGFR < 60 for the group with kidney dysfunction.

To assess the effect of kidney dysfunction on the small perforating branches of cerebral vessels, subgroup analysis was performed using the presence of SLI as a dependent variable.

All statistical analyses were conducted using the STATA software version 14.1 (StataCorp., TX); *p*-values < 0.05 were considered statistically significant.

3. Results

3.1. Baseline characteristics

The baseline characteristics and results from the univariate analysis are provided in Table 1. The mean age was 56.8 (±9.3) years, and 1422 (54.8%) subjects were male. The proportions of subjects taking anti-hypertensive, anti-diabetic, and anti-dyslipidemic drugs were 24.8%, 8.2%, and 10.3%, respectively. The mean systolic (125.2 mm Hg) and diastolic blood (75.6 mm Hg) pressures were under the lower limit of the definition of hypertension. The prevalence of hypertension, diabetes, and