Urine Protein Levels Predict Future Development of Cerebral Infarction in Koreans

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Purpose: Proteinuria is a clinical sign of adverse cardiovascular outcomes, including stroke. We aimed to assess the relationship between proteinuria and the occurrence of cerebral infarction.

Materials and Methods: In total, 208854 Koreans who participated in the 2009 medical examination were followed up until 2013 using the database of the National Health Insurance Service. The results of urine dipstick tests were utilized to assess proteinuria as absent, 1+, 2+, or ≥3+. The International Classification of Diseases code I63 was used to document cerebral infarction.

Results: Between 2009 and 2013, 2383 cases (1.14%) of cerebral infarction occurred during 912772.9 person-years of follow-up. Hazard ratios for incident cerebral infarction increased with inceasing amounts of urine protein from 1.53 (1.23–1.90) in group 2 (1+), 1.67 (1.22–2.28) in group 3 (2+), and 2.66 (1.79–3.96) in group 4 (≥3+), compared to the reference group with little to no detectable urine protein ($p<0.001$, respectively).

Conclusion: An increase in urine protein levels was significantly related to the risk of developing cerebral infarction. Our results suggest that proteinuria might be a potential risk factor for cerebral infarction and that urine dipstick test analysis may be clinically useful for predicting stroke.

Key Words: Proteinuria, cerebral infarction, cohort study, stroke, cardiovascular

INTRODUCTION

Proteinuria is emerging as a potential risk factor for cardiovascular diseases, including stroke.[1-4] A meta-analysis confirmed a robust relationship between proteinuria and stroke, wherein proteinuria increased the risk of stroke by 71%.[1,5] Another meta-analysis showed that the risk increased linearly with low estimated glomerular filtration rate (eGFR) and albuminuria, while an increase in albumin-creatinine ratio was related with a higher risk of subsequent stroke.[6] Further, clinical proteinuria above 300 mg/L was identified as a significant factor for stroke and coronary heart disease events regardless of other cardiovascular risk factors.[7]

Increased urinary protein excretion rates lead to generalized vascular dysfunction and damage. Proteinuria not only reflects renal damage but also leakage of lipoproteins into the vessel wall.[8-10] Lacunar infarction is a cerebral small vessel disease recorded in approximately 20%–25% of de novo ischemic strokes.[11-13] Although many advances have been made in identifying risk factors for multiple subtypes of stroke, including stroke due to macrovascular disease and cardiac embolic stroke, and understanding the pathophysiology of stroke, knowledge about the causes of lacunar stroke is limited.[14] Several studies have shown that blood-brain barrier dysfunction is an important part of cerebral small vessel diseases. Endothelial dysfunction may be the fundamental step in the deteriorating of lacunar infarction.[15-17]

Although studies have examined the correlation between proteinuria and a higher risk of stroke, associations between proteinuria and stroke subtype have rarely been investigated.[18]

It is also known that diabetes causes pathological changes in the blood vessels, increasing an individual's risk of stroke, and that when proteinuria occurs in patients with diabetes, the risk further increases.[19,20]

In this study, we aimed to confirm the relationship between proteinuria and clinically diagnosed cerebral infarction through an analysis of a large retrospective cohort of Koreans.

MATERIALS AND METHODS

Database

The Korean government operates a mandatory National Health Insurance system, which encompasses almost the entire population of Korea. Thus, the National Health Insurance Service (NHIS) database hold information on the health status of nearly all Koreans.[21] Medical health checkups are conducted to improve employees' health and strengthen the early detection of unrecognized diseases. All employees undergo medical checkups every 1 or 2 years under the Korea's Occupational Safety and Health Act. All data from checkups are deposited by the National Health Insurance Corporation (NHIC). Recently, a sample database of the NHIS has been provided for research after encrypting personal information. The NHIC sampled database includes information on checkups merged with the occurrence of cerebral infarction in Koreans statistical information service. Ethics approval was obtained from the Institutional Review Board of Kyung Hee University Hospital (IRB No: KHUH 2018-12-020). Since this was a retrospective study, the need for informed consent from the participants was waived by the Institutional Review Board.

Subjects

Of a total of 223551 medical health checkups in 2009, the data from 2387 who had ever been diagnosed with cerebral infarction (ICD-I63) between 2002 and the date before a medical health checkup in 2009 were excluded. Of the remaining 221164 participants, 12310 with factors that could influence cerebral infarction or urine protein were identified: no information on baseline urine protein levels in 2009 (n=772); presence of cancer code(s) (ICD C00–C97) between 2002 and 2009 on the day before the checkup (n=11574). A total of 208854 was finally included in the analysis, and the occurrence of cerebral infarction was observed. The total follow-up duration was 912772.9 person-years, and the average follow-up duration was 4.37 [standard deviation (SD), 0.48] years.

Stages of health checkup and laboratory measurement

The health checkups by the NHIC consisted of two stages. The first stage involved screening to identify disease among non-symptomatic general population. The second stage comprised more detailed examinations, including questionnaires on lifestyle or past medical information, etc. Overall, 10 indicators

were calculated from blood samples with the same data source and laboratory measurements. Further details are described in our previous article.[22] Urine protein levels were detected from a dipstick urine test. Urine analyses were based on a quantitative measurement of proteinuria as absent, 1+, 2+, or ≥3+.

Outcome definitions

Incident cerebral infarction was identified by reviewing the National Health Insurance database merged to Statistics Korea. The diagnosis of cerebral infarction was defined as the presence of the ICD-I63 code. From 2009 to 2013, participants with a newly registered ICD-I63 code were identified as having incident cerebral infarction.

Statistical analysis

Continuous variables are expressed as means±standard deviation or medians (intergroup range) and categorical variables as percentages. Baseline urine protein levels were analyzed using one-way ANOVA and the chi-square-test to identify differences between the participants at registration. Person-years were calculated as the sum of follow-up time from baseline to diagnosis of cerebral infarction or the last day of 2013.

To assess associations for incident cerebral infarction with baseline urine protein levels, Cox proportional hazards models were used to estimate adjusted hazard ratios (HRs) and 95% confidence intervals (CIs). Multivariate Cox proportional hazards models were developed with covariates identified as having a significant relationship between urine protein and incident cerebral infarction. The proportional hazard assumption was tested to confirm the validity of the Cox models. The assumption was assessed by a log minus log plot and found to not be graphically violated. The significance level was set at $p<0.05$. All the statistical analyses were performed using Statistical Analysis Software (version 9.4, SAS Institute, Cary, NC, USA).

RESULTS

Over a total of 912772.9 person-years of follow-up, the total number of incident cases of cerebral infarction during 2009–2013 was 2383 (1.14%). The baseline characteristics of the study groups according to urine protein levels are shown in Table 1. The absent group included individuals with negative or trace amounts of urine protein: 198097 participants (94.85%) correspond to negative and 4850 participants (2.32%) to trace. Statistically significant differences were identified between all of the variables and of baseline urine protein groups, except for low-density lipoprotein cholesterol and physical activity.

Participants with incident cerebral infarction were significantly older than those without, and metabolic profiles at baseline were less favorable. All clinical variables, except body mass index, total cholesterol, low-density lipoprotein cholesterol,

Table 1. Baseline Characteristics of the Participants according to Urine Protein Level (n=208854)

| Characteristic | Overall | Urine protein level | | | | p for trend* |
		Group 1 (absent; n=202947)	Group 2 (1+; n=3834)	Group 3 (2+; n=1578)	Group 4 (≥3+; n=495)	
Person-years (total)	912772.9	887499.8	16510.4	6710.5	2052.2	
Person-years (average)	4.37±0.48	4.37±0.47	4.31±0.65	4.25±0.72	4.15±0.84	<0.001
Age (yr)	57.7±8.6	57.7±8.6	59.4±9.2	59.3±9.1	61.4±9.3	<0.001
Sex						<0.001
Male	118034 (56.5)	114461 (56.4)	2279 (59.4)	977 (61.9)	317 (64.0)	
Female	90820 (43.5)	88486 (43.6)	1555 (40.6)	601 (38.1)	178 (36.0)	
BMI (kg/m^2)	24.0±2.9	24.0±2.9	24.5±3.2	24.8±3.4	24.7±3.5	<0.001
Systolic BP (mm Hg)	125.2±15.2	125.1±15.1	128.9±16.7	130.4±17.4	133.6±19.8	<0.001
Diastolic BP (mm Hg)	77.7±9.9	77.7±9.9	79.7±10.7	79.8±11.0	80.9±12.1	<0.001
Total cholesterol (mg/dL)	200.4±37.4	200.3±37.2	202.5±40.5	204.3±43.2	207.6±51.0	<0.001
Triglycerides (mg/dL)	118 (83–171)	118 (83–170)	131 (90–193)	136 (94–204)	148 (99–216)	<0.001
HDL-cholesterol (mg/dL)	55.4±32.2	55.5±32.4	53.5±23.0	53.7±26.6	51.7±26.0	0.011
LDL-cholesterol (mg/dL)	118.6±39.0	118.6±38.9	117.6±40.3	117.6±41.8	121.8±52.4	0.073
Fasting blood glucose (mg/dL)	100.7±25.2	100.3±24.5	111.5±37.8	116.3±43.7	122.9±47.9	<0.001
SCr (mg/dL)	1.15±1.49	1.14±1.45	1.33±1.89	1.45±3.08	1.63±2.78	<0.001
eGFR (mL/min/1.73 m^2)	80.9±20.2	81.1±20.0	75.7±22.6	72.2±23.9	65.7±25.8	<0.001
AST (U/L)	24 (20–29)	24 (20–29)	25 (20–31)	25 (20–33)	25 (20–33)	<0.001
ALT (U/L)	21 (16–29)	21 (16–29)	23 (16–33)	23 (16–34)	22 (16–33)	<0.001
GGT (U/L)	25 (17–41)	25 (17–41)	29 (19–52)	31 (20–60)	31 (20–55)	<0.001
Smoking amount (pack-years)	7.8±13.8	7.8±13.8	9.3±15.7	9.8±16.1	8.9±15.9	0.038
Alcohol intake (%)	14.6	14.6	17.4	18.6	15.2	<0.001
Physical activity (%)	16.8	16.8	17.0	17.6	15.9	0.770
Development of cerebral infarction (%)	2383 (1.14)	2228 (1.10)	89 (2.32)	41 (2.60)	25 (5.05)	<0.001

ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; GGT, gamma-glutamyl transferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SCr, serum creatinine.
Data are presented as a mean±standard deviation, median (intergroup range), or n (%), as appropriate.
*p value by analysis of variance test for continuous variables and the chi-square test for categorical variables.

serum creatinine, and aspartate transaminase, showed statistically significant differences between the two groups as expected (Supplementary Table 1, only online).

The HRs and 95% CI of cerebral infarction occurrence according to urine protein levels are shown in Table 2. In the unadjusted model, the HRs and 95% CI for incident cerebral infarction were 2.15 (1.74–2.66) in group 2 (1+), 2.45 (1.80–3.33) in group 3 (2+), and 4.91 (3.31–7.28) in group 4 (≥3+), compared to the reference group with little to no detectable urine protein (group 1, p for all <0.001). In the multivariate adjusted model, these associations remained statistically significant even after additional adjustment of covariates. The adjusted HRs and 95% CIs were 1.53 (1.23–1.90), 1.67 (1.22–2.28), and 2.66 (1.79–3.96), respectively (p<0.001).

DISCUSSION

This large retrospective cohort study demonstrated that the risk of cerebral infarction in Koreans tended to increase as urine protein levels increased over a 5-year tracking period. The findings in this study are in line with previously published results. A previous cohort study conducted in China also showed that proteinuria levels were associated with stroke onset. An increased stroke risk [HR 1.46 (95% CI, 1.26–1.68) and HR 1.71 (95% CI, 1.42–2.06)] was found with the occurrence of proteinuria and persistent proteinuria, compared to the absence of proteinuria. The effect size for risk of stroke subtypes, including ischemic and hemorrhagic variants, was similar. One of the differences from our study is that this analysis was performed according to whether proteinuria persisted for 2 years without classification according to proteinuria stage.[23] A 27-year follow-up study of the Honolulu Heart Program revealed that proteinuria levels on urine dipstick screening independently predicted an increased risk for stroke.[9] A recent study of hypertension confirmed that baseline proteinuria using dipstick or urine albumin/creatinine ratio is independently associated with an elevated risk of first incident stroke and ischemic stroke, even if eGFR is not reduced.[24] In addition, a meta-analysis of cohort studies and randomized controlled trials showed that albuminuria was associated with greater stroke risk.[6]

Stroke is one of the leading causes of death and disability

Table 2. HRs and 95% CIs of the Incidence of Cerebral Infarction according to Urine Protein Level

	Person-years	Incident cases	Incidence density (per 10000 person-years)	HR (95% CI)	
				Unadjusted	Multivariate adjusted model*
Urine protein levels					
Group 1	887499.8	2228	25.1	1.00 (reference)	1.00 (reference)
Group 2	16510.4	89	53.9	2.15 (1.74–2.66)	1.53 (1.23–1.90)
Group 3	6710.5	41	61.1	2.45 (1.80–3.33)	1.67 (1.22–2.28)
Group 4	2052.2	25	121.8	4.91 (3.31–7.28)	2.66 (1.79–3.96)
P for trend				<0.001	<0.001
Age					1.10 (1.09–1.10)
Sex (female vs. male)					0.72 (0.66–0.80)
BMI					1.01 (1.00–1.03)
Systolic BP					1.012 (1.010–1.015)
Fasting blood glucose					1.006 (1.005–1.007)
LDL-cholesterol					1.002 (1.001–1.003)
GGT					1.001 (1.000–1.002)
eGFR					0.997 (0.995–0.999)
Smoking amount (pack-years)					1.007 (1.004–1.010)
Alcohol intake					0.983 (0.871–1.109)
Physical activity					0.851 (0.759–0.955)

BP, blood pressure; BMI, body mass index; CI, confidence intervals; eGFR, estimated glomerular filtration rate; GGT, gamma-glutamyl transferase; HR, hazard ratios; LDL, low-density lipoprotein.
*The multivariate adjusted model was adjusted for age, BMI, systolic BP, fasting blood glucose, LDL-cholesterol, GGT, eGFR, smoking amount (pack-years), alcohol intake, and physical activity.

worldwide, contributing not merely to mortality but also to an increased burden of disease on survivors and their families.[25] Stroke-related prevalence and medical costs have increased steadily over the past decade.[26] Therefore, an increase in the burden of disease due to stroke suggests that early detection and prevention of stroke risk factors are important in an aging and/or aged population.[27] In the case of cerebral infarction, intracranial atherosclerosis is a strong prognostic factor, and advanced atherosclerotic plaque, although asymptomatic, may still have poor clinical outcomes.[27]

Urine protein is highly correlated with eGFR and serum creatinine. Our results showed that cerebral infarction was associated with amounts of urine protein and eGRF, but not with serum creatinine. Serum creatinine is most widely used in kidney function evaluation, but can be affected by several factors, such as age, sex, race, nutritional status, and body muscle mass.[28] Unlike eGFR, studies have yet to establish an association between serum creatinine and ischemic stroke.[29]

Proteinuria plays an important role in the pathophysiology of lipid disorders in nephrotic syndrome and may be a sensitive marker of systemic factors that reflect the atherosclerotic process.[9,10,30] Proteinuria detected on a dipstick urinalysis has been reported to be an important prediction of mortality after acute ischemic stroke.[31] It is necessary for physicians and health care professionals to know that the risk of stroke can be reduced through the early detection and control of proteinuria. The urinary dipstick test is a quick and simple clinical tool to find proteinuria and may be of use in identifying patients at high risk of

mortality.[32] Few reports have demonstrated a significant correlation between the results of dipstick proteinuria test and cerebral infarction in a general population. It is meaningful that our study demonstrated that proteinuria detected using the dipstick is an independent predictor for cerebral infarction through 5 years of follow-up.

The results of this research should be interpreted in consideration of some inherent limitations. First, urinary protein was evaluated by only a single urine collection from each participant. The lack of periodic follow-up of proteinuria measurements after the baseline period is a weakness of this study. Second, collection bias may exist because raw data were collected from medical examinations and related surveys in this study. Third, the tracking period of the study subjects was only 4.37 years, and there was a limit to evaluating the long-term impacts of proteinuria on cerebral infarction. Fourth, the use of cardio-protective medication and comorbidity may be important factors in incident cerebral infarction. However, the exclusion criteria for this study did not include a prior history of cardiovascular disease or the use of antiplatelet or anticoagulants. Lastly, despite the convenience and accessibility of urine dipstick proteinuria, the sensitivity and specificity of urine dipstick tests are low. Therefore, the usefulness of quantifying urine protein in clinical evaluation is limited. Further research will be needed to overcome these limitations.

In conclusion, our findings demonstrated that proteinuria may be an important risk factor or early predictor of cerebral infarction. This association was significantly related to the risk

of cerebral infarction, regardless of other vascular risk factors, such as fasting blood glucose, body mass index, and systolic blood pressure. Understanding the clinical significance of measuring proteinuria using dipstick testing for predicting cerebral infarction may provide meaningful understanding for preventing medical complications related to cerebral infarction.

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AUTHOR CONTRIBUTIONS

Conceptualization: Jae-Hong Ryoo. Data curation: all authors. Formal analysis: Eunhee Ha and Jae-Hong Ryoo. Funding acquisition: Jae-Hong Ryoo. Investigation: all authors. Methodology: all authors. Project administration: Jae-Hong Ryoo. Resources: all authors. Software: Eunhee Ha. Supervision: Jae-Hong Ryoo. Validation: all authors. Visualization: Jae-Hong Ryoo. Writing—original draft: Sang Min Lee. Writing—review & editing: all authors. Approval of final manuscript: all authors.

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