Original Contribution

Insulin Resistance Is a Risk Factor for Silent Lacunar Infarction

Ji Eun Lee, MD, MPH; Dong Wook Shin, MD, PhD; Jae Moon Yun, MD, MPH; Sang Hyuck Kim, MD; You-Seon Nam, MD; BeLong Cho, MD, MPH, PhD; Jae-Sung Lim, MD; Han-Yeong Jeong, MD; Hyung-Min Kwon, MD, PhD; Jin-Ho Park, MD, PhD

Background and Purpose—This study aims to investigate the association between insulin resistance (IR) and silent lacunar infarction (SLI) in healthy adults.

Methods—We recruited 2326 healthy Korean adults who took health checkups, including a brain magnetic resonance imaging. SLI was defined as an infarction measuring 0.3 to 1.5 cm in diameter that was localized in the territory of perforating branches of cerebral arteries, as seen in the brain magnetic resonance imaging. The homeostasis model assessment–estimated insulin resistance index was used for IR estimation, and the cutoff value for its diagnosis for Koreans was 2.56.

Results—The mean age of the study population was 56.2 years (range, 40–79 years), and 1279 subjects (55.0%) were male. The prevalence of SLI and IR was 8.1% and 18.1%, respectively. In multivariate logistic analysis, after adjusting for traditional SLI-associated risk factors, IR was positively associated with the prevalence of SLI (adjusted odds ratio, 1.69; 95% confidence interval, 1.16–2.46). The proportion of subjects with multiple SLI lesions (≥2) was also higher in the IR (+) group than that in the IR (−) group (4.3% versus 1.7%; $P<0.001$). In ordered logistic regression, IR was positively associated with an increase in SLI severity (adjusted odds ratio, 1.76; 95% confidence interval, 1.21–2.56).

Conclusions—IR is an independent risk factor of SLI presence and its severity in Koreans. Whether improvement of IR might prevent SLI occurrence needs to be addressed by clinical trials. **(*Stroke*. 2016;47:00-00. DOI: 10.1161/STROKEAHA.116.014097.)**

Key Words: infarction ■ insulin resistance ■ magnetic resonance imaging ■ multivariate analysis ■ stroke

Silent brain infarction (SBI) is a common incidental finding on brain magnetic resonance imaging (MRI). Until recently, this finding had been considered a benign accompaniment to aging.[1] However, accumulating evidences have shown that SBI is a clinically important precursor lesion of many adverse health outcomes, including cognitive decline[2] and clinical stroke.[3]

SBI includes 2 subtypes, lacunar type (silent lacunar infarction [SLI]) and nonlacunar type.[4] Nonlacunar type is thought to result from an embolism or atherosclerotic stenosis.[5] Although there are some known risk factors for lacunar infarction, such as old age and hypertension,[6,7] the risk of others is not yet clear.

Among other risk factors, diabetes mellitus has been recently recognized as a risk factor for symptomatic lacunar infarction, but not for SLI.[8] Meanwhile, some recent studies have suggested that metabolic syndrome is a risk factor for SLI.[9,10]

Because insulin resistance (IR) is a well-known core feature of metabolic syndrome occurrence,[11] the relation between metabolic syndrome and SLI from previous studies[9,10] suggested a meaningful association of IR and SLI. In addition, some recent studies suggested that IR was related to a risk of SLI occurrence.[12,13] As for stroke, some studies revealed that IR increases the risk for clinical stroke.[14,15] However, there is still a lack of research confirming the association of IR and SLI.

The objective of this study is to investigate whether IR is associated with SLI, independent of other clinical risk factors for SLI development.

Methods

Study Population

A total of 2366 subjects aged 40 to 79 years, who took routine voluntary health checkups, including brain MRI, for early disease detection and prevention from January 2006 to January 2014 at Seoul National

Received May 22, 2016; final revision received September 24, 2016; accepted October 5, 2016.

From the Department of Family Medicine (J.E.L., D.W.S., J.M.Y., S.H.K., Y.-S.N., B.C., J.-H.P.) and Health Promotion Center (J.E.L., D.W.S., J.M.Y., S.H.K., Y.-S.N., B.C., J.-H.P.), Seoul National University Hospital, Republic of Korea; Department of Neurology, Hallym University Sacred Heart Hospital, Anyang, Republic of Korea (J.-S.L.); Department of Neurology, Aerospace Medical Center, Cheongju, Republic of Korea (H.-Y.J.); and Department of Neurology, Seoul National University-Seoul Municipal Government Boramae Medical Center, Republic of Korea (H.-M.K.).

The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.116.014097/-/DC1.

Correspondence to Jin-Ho Park, MD, PhD, Department of Family Medicine, Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Seoul 03080, Republic of Korea, E-mail kkolzzi0@gmail.com or Hyung-Min Kwon, MD, PhD, Department of Neurology, Seoul National University-Seoul Municipal Government Boramae Medical Center, 20 Boramae-ro 5-gil, Dongjak-gu, Seoul 07061, Republic of Korea, E-mail hmkwon@snu.ac.kr

Stroke **is available at http://stroke.ahajournals.org** **DOI: 10.1161/STROKEAHA.116.014097**

University Hospital Health Promotion Center, were recruited. All the examinations were taken at the same day. Among them, 40 subjects who had reported previous stroke were excluded. Subjects with previous stroke were defined as either having reported that they had previous confirmed clinical stroke or reported taking medication for stroke in a self-completion questionnaire. Finally, 2326 subjects were included in the analysis. The study was approved by the institutional review board at Seoul National University Hospital (Institutional Review Board No 1502-026-647).

Baseline Data Collection

Clinical information, including age, sex, smoking status, comorbid conditions, and medications related to hypertension, diabetes mellitus, and dyslipidemia, were obtained by a self-completion questionnaire. In addition, the subjects who were taking aspirin, clopidogrel, warfarin, or other antiplatelet drugs were identified. Blood tests were done after 12 hours of overnight fasting to measure glucose, insulin, creatinine, and total cholesterol levels. Blood pressure was measured after resting for >5 minutes in the sitting position. Subjects were considered to have hypertension if they had a high systolic (≥140 mm Hg) or diastolic (≥90 mm Hg) blood pressure[16] or were currently taking antihypertensive medications. Subjects with a total cholesterol level of ≥240 mg/dL or currently taking lipid-lowering agents were considered to have hypercholesterolemia.[17] Diabetes mellitus was defined as hemoglobin A1c ≥6.5%, fasting glucose ≥126 mg/dL,[18] or being on diabetes mellitus medication. Kidney function was estimated from the Modification of Diet in Renal Disease (MDRD) formula, which was staged according to the chronic kidney disease categorization of the US National Kidney Foundation, as normal (≥90) renal function or mild (60–89.9), moderate (30–59.9), and severe (<30 mL/min per 1.73 m^2) renal dysfunction.[19] The body mass index (BMI) was calculated as weight (kg) divided by the height squared (m^2). Overweight (BMI, 23.0–24.9) and obesity (BMI ≥25.0) were defined according to the World Health Organization criteria for the Asia-Pacific region.[20]

Definition of IR

IR was estimated using the homeostasis model assessment–estimated insulin resistance (HOMA-IR) index, which is widely used for the estimation of IR in clinical and epidemiological research.[21,22] HOMA-IR was calculated by multiplying glucose (mg/dL) by insulin (μU/mL) and dividing by 405.[23] The cutoff value of 2.56 was used to diagnose for IR, as previously reported in Korean adults.[24] In addition, we used the HOMA-IR criteria from the Japan Diabetes Society,[25,26] in which HOMA-IR ≤1.60 indicates non-IR and HOMA-IR ≥2.50 is regarded as IR, as another representative criteria in Eastern Asia.

Diagnosis of SLI

SLI was defined as a focal infarction, which was 0.3 to 1.5 cm in diameter and in the territory of perforating branches to the basal ganglia, thalamus, internal capsule, corona radiate, centrum semiovale, brain stem, or cerebellum, that had central signal intensity corresponding to the cerebrospinal fluid on T1- and T2-weighted images in MRI examinations. Lesions were differentiated on fluid-attenuated inversion recovery from periventricular white matter lesions, which were of high signal intensity. Dilated perivascular spaces were distinguished from SLI based on their locations (along perforating or medullary arteries, often bilaterally symmetrical, usually in the lower third of the basal ganglia) and by the absence of gliosis. The MRI were independently evaluated by 2 neurologists (J.-S.L. and H.-M.K.). MRI was performed at 1.5-T field strength (Signa, GE Healthcare, Milwaukee, WI, or Magnetom SONATA, Siemens, Munich, Germany). The imaging protocol consisted of T2-weighted fast spin-echo (repetition time/echo time=5000/127 ms), T1-weighted spin-echo (repetition time/echo time=500/11 ms), and fluid-attenuated inversion recovery imaging (repetition time/echotime=8800/127 ms; inversion time=2250 ms). Images were obtained as 26 transaxial slices per scan. The slice thickness was 5 mm, with a 1-mm interslice gap. In addition, the volume of white matter hyperintensity (WMH) was assessed. The MRI from January 2006 to December 2011 (n=1671) were reviewed by 1 reader (H.-Y.J.), who was blinded to clinical data. Scans were converted from DICOM to Analyze format, using MRIcro software (University of Nottingham School of Psychology, Nottingham, United Kingdom; http://www.mricro.com), for computer-assisted determination of WMH volume.[27] Signal intensity thresholding, followed by manual editing, was used to create a region-of-interest map of supratentorial WMHs. Axial T2–fluid-attenuated inversion recovery sequences were used to create the WMH maps.

Statistics

Data were summarized as numbers with percentages for categorical variables and mean values with standard deviation for continuous variables. For each demographic and clinical feature by the SLI status, we performed a group-wise comparison using the Student *t* test for continuous variables and the χ^2 test for categorical variables (Table 1). Univariate logistic regression was used to evaluate the association of each variable and presence of SLI (Table 2). For multivariate analysis, we included the following risk factors that were considered in previous studies,[6,7] namely, age, sex, hypertension, hypercholesterolemia, diabetes mellitus, smoking, BMI, chronic kidney disease, medications that might affect IR or SLI, antidiabetic and antiplatelet medication, and C-reactive protein. Three models were defined for multivariate analyses. Model 1 divided subjects according to antidiabetic medication and adjusted for it. Model 2 divided subjects according to diabetes mellitus status. Model 3 excluded subjects with diabetes mellitus. These models were applied to all multivariate analyses of this study. We used ordered logistic regression to assess the association between IR and the increasing number of SLI lesions (Table 3). When the dependent variable is ordinal, this statistical method gives cumulative probabilities as odds ratios.[28] In this model, the dependent variable has multiple cutoff levels (eg, SLI lesion 1, ≥2 versus 0 and ≥ 2versus 0, 1). A single equation is estimated over the levels of the dependent variable, and a cumulative odds ratio is calculated from the equation. It is assumed that the odds ratios of each cutoff level are about the same with the calculated odds ratio (proportional odds assumption). In addition, the proportions of subjects with each number of SLI lesions 1, ≥2, and a total by IR groups were compared by χ^2 test (Figure). Linear regression was applied to evaluate the association between each variable and the volume of WMH (Table I in the online-only Data Supplement). In addition, multivariate logistic regression, using another HOMA-IR cutoff level by the Japan Diabetes Society criteria, was conducted (Table II in the online-only Data Supplement). The association between continuous HOMA-IR level and presence of SLI was also analyzed by multivariate logistic regression (Table III in the online-only Data Supplement).

Results

Study Population Characteristics

Among the total 2326 subjects who were included in the analysis, 18.1% showed IR (HOMA-IR≥2.56). The proportion of subjects with IR was higher in the group that had SLI than that in the group without SLI (27.7% versus 17.3%; $P<0.001$). And the mean level of HOMA-IR was also higher in SLI (+) group than in SLI (−) group (2.1 versus 1.7; $P=0.002$). Fasting glucose and fasting insulin levels were also higher in the SLI (+) group. As for age distribution, the mean age was significantly higher in the SLI (+) group than in the SLI (−) group (62.2 versus 55.6; $P<0.001$). The proportions of hypertension, diabetes mellitus, and chronic kidney disease were higher in the SLI (+) group than in the SLI (−) group (all $P<0.01$). The distribution of other cardiovascular risk factors and medications did not show significant differences between the 2 groups (Table 1).

Table 1. Study Population Characteristics by SLI status and Comparison of Cardiovascular Risk Factors

	Total (n=2326)	Presence of SLI		*P* Value*
		Yes (n=188)	No (n=2138)	
Age				
Mean±SD	56.2±9.0	62.2±8.6	55.6±8.9	<0.001
Sex, n (%)				
Female	1047 (45.0)	87 (46.3)	960 (44.9)	0.716
Male	1279 (55.0)	101 (53.7)	1178 (55.1)	
Smoking, n (%)				
Never or former	1878 (80.7)	159 (84.6)	1719 (80.4)	0.164
Current	448 (19.3)	29 (15.4)	419 (19.6)	
Body mass index, kg/m^2, n (%)				
<23	843 (36.2)	70 (37.2)†	773 (36.2)	0.895
≥23, <25	665 (28.6)	51 (27.1)	614 (28.7)	
≥25	818 (35.2)	67 (35.6)	751 (35.1)	
HOMA-IR, n (%)				
<2.56	1905 (81.9)	136 (72.3)	1769 (82.7)	<0.001
≥2.56	421 (18.1)	52 (27.7)	369 (17.3)	
Mean±SD	1.8±1.3	2.1±2.1	1.7±1.2	0.002
Fasting blood glucose				
Mean±SD	95.8±22.1	99.8±25.5	95.5±21.7	0.008
Insulin				
Mean±SD	7.3±4.7	8.2±6.8	7.2±4.5	0.009
Hypertension, n (%)‡				
No	1435 (61.7)	82 (43.6)	1353 (63.3)	<0.001
Yes	891 (38.3)	106 (56.4)	785 (36.7)	
Hypercholesterolemia, n (%)§				
No	1852 (79.6)	149 (79.3)	1703 (79.7)†	0.897
Yes	474 (20.4)	39 (20.7)	435 (20.4)	
Diabetes mellitus, n (%)‖				
No	1992 (85.6)	144 (76.6)	1848 (86.4)	<0.001
Yes	334 (14.4)	44 (23.4)	290 (13.6)	
Chronic kidney disease, n (%)¶				
Normal	464 (20.0)†	34 (18.1)	430 (20.1)	0.004
Mild	1683 (72.4)	128 (68.1)	1555 (72.7)	
Moderate to severe	179 (7.7)	26 (13.8)	153 (7.2)	
Antidiabetic medication, n (%)				
No	2163 (93.0)	170 (90.4)	1993 (93.2)	0.150
Yes	163 (7.0)	18 (9.6)	145 (6.8)	
Anticoagulation or antiplatelet medication, n (%)#				
No	2097 (90.2)†	163 (86.7)	1934 (90.5)	0.097
Yes	229 (9.9)	25 (13.3)	204 (9.5)	
C-reactive protein, mg/dL				
Mean±SD	0.2±0.7	0.3±0.9	0.2±0.7	0.191

HOMA-IR indicates homeostasis model assessment–estimated insulin resistance; and SLI, silent lacunar infarction.

*Comparison was performed between with and without SLI groups. The Student *t* test was used for continuous variables and χ^2 test for categorical variables. Mean values of HOMA-IR, glucose, and insulin were compared after square root transformation.

†Total percentages may not equal 100% because of rounding.

‡Those who were taking antihypertensive drugs or had a systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg.

§Those who were taking lipid-lowering drugs or had a total cholesterol level ≥240 mg/dL.

‖Those who were taking antidiabetic medications or hemoglobin A1c ≥6.5% or fasting glucose ≥126 mg/dL.

¶Normal: stage 1, mild: stage 2, moderate to severe: stages 3, 4, and 5 by chronic kidney disease stages of the US National Kidney Foundation.

#Those who were taking aspirin, clopidogrel, warfarin, or other antiplatelet drugs.

Association Between IR and Presence of SLI

In model 1, after adjustment for possible other risk factors of SLI, IR was positively associated with the presence of SLI (adjusted odds ratio [aOR], 1.69; 95% confidence interval [CI], 1.16–2.46; *P*=0.006). Among the other factors, aging (aOR, 1.08; 95% CI, 1.06–1.10; *P*<0.001) and hypertension (aOR, 1.76; 95% CI, 1.27–2.43; *P*=0.001) increased the likelihood of SLI. In model 2, in which diabetes mellitus was included, IR was still positively associated with the presence of SLI (aOR, 1.60; 95% CI, 1.09–2.35; *P*<0.015). The same association was observed after exclusion of diabetes mellitus patients in model 3 (aOR, 1.64; 95% CI, 1.04–2.59; *P*<0.033; Table 2).

When the Japanese criteria were applied, the same association between IR and SLI was observed in all the 3 models (model 1; aOR, 1.78; 95% CI, 1.19–2.66; *P*=0.005; and aOR, 1.20; 95% CI, 0.82–1.77; *P*=0.353 for HOMA-IR ≥2.50 and >1.60, <2.50, respectively; Table II in the online-only Data Supplement). In a multivariate logistic analysis using continuous HOMA-IR level, the same positive association was observed (model 1; aOR, 1.57; 95% CI, 1.10–2.24; *P*=0.014; Table III in the online-only Data Supplement).

Association Between IR and Multiple SLI

When compared with subjects without IR, subjects with IR showed a higher prevalence of one SLI lesion (8.1% versus 5.5%) and multiple SLI lesions (4.3% versus 1.7%). The association was statistically significant in a χ^2 test (*P*<0.001; Figure).

Association Between IR and Increasing Number of SLI

We assessed the association between IR and the increasing number of SLI using ordered logistic regression. In a univariate analysis, when 1 unit of IR increased (<2.56 to ≥2.56), odds ratios for the presence of SLI (1, ≥2 versus 0) and for 2

Table 2. Association of Insulin Resistance and Other Cardiovascular Risk Factors With Presence of SLI

	Univariate Analysis*		Model 1		Model 2		Model 3	
	OR (95% CI)	*P* Value	aOR (95% CI)	*P* Value	aOR (95% CI)	*P* Value	aOR (95% CI)	*P* Value
HOMA-IR ≥2.56	1.83 (1.31–2.57)	<0.001	1.69 (1.16–2.46)	0.006	1.60 (1.09–2.35)	0.015	1.64 (1.04–2.59)	0.033
Age (1-year difference)	1.09 (1.07–1.11)	<0.001	1.08 (1.06–1.10)	<0.001	1.08 (1.06–1.10)	<0.001	1.07 (1.05–1.10)	<0.001
Sex (male)	0.95 (0.70–1.28)	0.716	0.91 (0.65–1.27)	0.562	0.90 (0.64–1.26)	0.532	1.02 (0.70–1.49)	0.898
Hypertension†	2.23 (1.65–3.01)	<0.001	1.76 (1.27–2.43)	0.001	1.74 (1.26–2.41)	0.001	1.73 (1.20–2.50)	0.003
Hypercholesterolemia‡	1.02 (0.71–1.48)	0.897	0.87 (0.59–1.27)	0.467	0.86 (0.58–1.26)	0.434	0.85 (0.54–1.33)	0.474
Diabetes mellitus§	1.95 (1.36–2.79)	<0.001			1.19 (0.80–1.78)	0.384		
Smoking‖	0.75 (0.50–1.13)	0.166	1.17 (0.74–1.85)	0.498	1.14 (0.72–1.81)	0.565	0.88 (0.50–1.55)	0.658
Body mass index, kg/m^2								
<23	1.00		1.00		1.00		1.00	
≥23, <25	0.92 (0.63–1.34)	0.653	0.85 (0.57–1.26)	0.417	0.85 (0.57–1.25)	0.404	0.83 (0.53–1.29)	0.403
≥25	0.99 (0.69–1.40)	0.933	0.81 (0.55–1.19)	0.287	0.81 (0.55–1.20)	0.303	0.83 (0.53–1.28)	0.398
Chronic kidney disease¶								
Normal	1.00		1.00		1.00		1.00	
Mild	1.04 (0.70–1.54)	0.841	0.86 (0.57–1.30)	0.474	0.88 (0.58–1.32)	0.524	0.80 (0.50–1.26)	0.328
Moderate to severe	2.15 (1.25–3.70)	0.006	1.16 (0.65–2.08)	0.614	1.16 (0.64–2.07)	0.627	1.20 (0.62–2.33)	0.592
Antidiabetic medication	1.46 (0.87–2.43)	0.153	0.88 (0.50–1.52)	0.639				
Anticoagulation or antiplatelet medication#	1.45 (0.93–2.27)	0.099	0.92 (0.57–1.48)	0.721	0.87 (0.54–1.41)	0.582	0.73 (0.39–1.36)	0.324
C-reactive protein, mg/dL	1.10 (0.95–1.27)	0.207	1.02 (0.86–1.20)	0.854	1.01 (0.85–1.19)	0.931	1.01 (0.80–1.27)	0.961

aOR indicates adjusted odds ratio; CI, confidence interval; HOMA-IR, homeostasis model assessment–estimated insulin resistance; OR, odds ratio; and SLI, silent lacunar infarction.

*ORs and *P* values were calculated using logistic regression analysis. models 1–3 are multivariate analysis models including each of the following variables: model 1: HOMA-IR, age, sex, hypertension, hypercholesterolemia, smoking, body mass index, chronic kidney disease stage, antidiabetic medication, anticoagulation or antiplatelet medication, and C-reactive protein; model 2: HOMA-IR, age, sex, hypertension, hypercholesterolemia, diabetes mellitus, smoking, body mass index, chronic kidney disease stage, anticoagulation or antiplatelet medication, and C-reactive protein; model 3: HOMA-IR, age, sex, hypertension, hypercholesterolemia, smoking, body mass index, chronic kidney disease stage, anticoagulation or antiplatelet medication, and C-reactive protein. Diabetes mellitus patients were excluded in model 3.

†Those who were taking antihypertensive drugs or systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg.

‡Those who were taking lipid-lowering drugs or total cholesterol ≥240 mg/dL.

§Those who were taking antidiabetic medications or hemoglobin A1c ≥6.5% or fasting glucose ≥126 mg/dL.

‖Current smokers.

¶Normal: stage 1, mild: stage 2, moderate to severe: stages 3, 4, and 5 by chronic kidney disease stages of the US National Kidney Foundation.

#Those who were taking aspirin, clopidogrel, warfarin, or other antiplatelet medication.

or more SLI (≥2 versus 0, 1) were 1.86 (95% CI, 1.32–2.60; *P*<0.001). In this statistical model, the same odds ratio is presumed for each level. This tendency was maintained in all the multivariate models (model 1: aOR, 1.76; 95% CI, 1.21–2.56; *P*=0.003; model 2: aOR, 1.66; 95% CI, 1.14–2.43; *P*=0.009; model 3: aOR, 1.68; 95% CI, 1.06–2.64; *P*=0.026). The results imply that IR increases the likelihood of increasing numbers of SLI (Table 3).

Association Between IR and Volume of WMH

The results of the univariate analysis demonstrated a positive association between HOMA-IR and the volume of WMH (coefficient, 0.16; 95% CI, 0.03–0.29; *P*=0.019). However, this association was not significant in the 3 multivariate models (model 1: coefficient, 0.10; 95% CI, −0.03 to 0.23; *P*=0.117; model 2: coefficient, 0.08; 95% CI, −0.05 to 0.21; *P*=0.235; model 3: coefficient, 0.08; 95% CI, −0.07 to 0.23; *P*=0.298). Among the other covariates, in the multivariate models, age and hypertension showed a positive association with the volume of WMH, whereas BMI was negatively associated (Table I in the online-only Data Supplement).

Discussion

In this study, we investigated the association between IR and SLI using detailed demographic, lifestyle, clinical, and medication factors in screened Korean adults. We found that IR was independently associated with both the presence and the severity of SLI using an appropriate multivariate analysis adjusted for known SLI-related risk factors.

Until now, there have been some studies on associations of traditional cardiovascular risk factors constituting metabolic syndrome and metabolic syndrome itself and SLI.[9,10] However, there has been lack of research on the association of IR and SLI. A recent study demonstrated that thiazolidinedione,

Table 3. Association of Insulin Resistance and Other Cardiovascular Risk Factors With Increasing Number of SLI Occurrence

	Univariate Analysis*		Model 1		Model 2		Model 3	
	OR (95% CI)	*P* Value	aOR (95% CI)	*P* Value	aOR (95% CI)	*P* Value	aOR (95% CI)	*P* Value
HOMA-IR ≥2.56	1.86 (1.32–2.60)	<0.001	1.76 (1.21–2.56)	0.003	1.66 (1.14–2.43)	0.009	1.68 (1.06–2.64)	0.026
Age (1-year difference)	1.09 (1.07–1.11)	<0.001	1.09 (1.07–1.11)	<0.001	1.08 (1.06–1.11)	<0.001	1.08 (1.05–1.10)	<0.001
Sex (male)	0.96 (0.71–1.29)	0.765	0.90 (0.65–1.26)	0.555	0.90 (0.64–1.26)	0.532	1.02 (0.70–1.49)	0.906
Hypertension†	2.24 (1.66–3.03)	<0.001	1.79 (1.29–2.47)	<0.001	1.77 (1.28–2.44)	0.001	1.76 (1.22–2.53)	0.003
Hypercholesterolemia‡	1.02 (0.71–1.47)	0.913	0.86 (0.58–1.26)	0.430	0.85 (0.58–1.24)	0.395	0.84 (0.53–1.31)	0.440
Diabetes mellitus§	1.98 (1.38–2.83)	<0.001			1.20 (0.80–1.78)	0.376		
Smoking‖	0.75 (0.50–1.14)	0.176	1.25 (0.79–1.97)	0.339	1.22 (0.77–1.92)	0.398	0.91 (0.52–1.60)	0.748
Body mass index, kg/m^2								
<23	1.00		1.00		1.00		1.00	
≥23, <25	0.91 (0.62–1.32)	0.610	0.81 (0.55–1.20)	0.296	0.81 (0.54–1.20)	0.287	0.80 (0.51–1.25)	0.323
≥25	0.98 (0.69–1.39)	0.903	0.78 (0.53–1.15)	0.211	0.79 (0.53–1.16)	0.228	0.80 (0.52–1.25)	0.330
Chronic kidney disease¶								
Normal	1.00		1.00		1.00		1.00	
Mild	1.05 (0.71–1.56)	0.807	0.86 (0.57–1.30)	0.481	0.88 (0.58–1.33)	0.543	0.80 (0.50–1.26)	0.332
Moderate to severe	2.24 (1.30–3.85)	0.004	1.27 (0.71–2.27)	0.414	1.27 (0.71–2.26)	0.424	1.26 (0.65–2.44)	0.493
Antidiabetic medication	1.46 (0.87–2.43)	0.151	0.84 (0.48–1.47)	0.550				
Anticoagulation or antiplatelet medication#	1.45 (0.93–2.26)	0.103	0.90 (0.56–1.45)	0.667	0.85 (0.53–1.37)	0.506	0.73 (0.39–1.36)	0.326
C-reactive protein, mg/dL	1.10 (0.95–1.28)	0.185	1.02 (0.87–1.21)	0.784	1.01 (0.86–1.20)	0.880	1.02 (0.81–1.29)	0.852

aOR indicates adjusted odds ratio; CI, confidence interval; HOMA-IR, homeostasis model assessment–estimated insulin resistance; OR, odds ratio; and SLI, silent lacunar infarction.

*ORs and *P* values were calculated using ordered logistic regression for 3 ordered categories according to number of SLI (0, 1, and ≥ 2). Models 1–3 are multivariate analysis models including each of the following variables: model 1: HOMA-IR, age, sex, hypertension, hypercholesterolemia, smoking, body mass index, chronic kidney disease stage, antidiabetic medication, anticoagulation or antiplatelet medication, and C-reactive protein; model 2: HOMA-IR, age, sex, hypertension, hypercholesterolemia, diabetes mellitus, smoking, body mass index, chronic kidney disease stage, anticoagulation or antiplatelet medication, and C-reactive protein; model 3: HOMA-IR, age, sex, hypertension, hypercholesterolemia, smoking, body mass index, chronic kidney disease stage, anticoagulation or antiplatelet medication, and C-reactive protein. Diabetes mellitus patients were excluded in model 3.

†Those who were taking antihypertensive drugs or SBP ≥140 mm Hg or DBP ≥90 mm Hg.

‡Those who were taking lipid-lowering drugs or total cholesterol ≥240 mg/dL.

§Those who were taking antidiabetic medications or hemoglobin A1c ≥6.5% or fasting glucose ≥126 mg/dL.

‖Current smokers.

¶Normal: stage 1, mild: stage 2, moderate to severe: stages 3, 4, and 5 by chronic kidney disease stages of the US National Kidney Foundation.

#Those who were taking aspirin, clopidogrel, warfarin, or other antiplatelet medication.

whose main mechanism is the reduction of IR, decreased the risk of stroke recurrence.[13] This result implied that IR may be a risk factor in the development of SLI. Another recent study with 934 participants from the Atherosclerosis Risk in Communities (ARIC) study, who completed 2 brain MRI with a 10-year interval, reported positive association between IR and new lacunar lesions.[12] Although it used study population-specific IR score as an IR estimation index, it first investigated prospectively the relationship of IR and future occurrence of lacunar infarction and demonstrated possible causal relationship between IR and lacunar infarction. In addition to above study findings, our findings give strong additional evidence to the association between IR and lacunar lesions.

IR is a hallmark of many cardiovascular diseases.[29,30] IR causes type 2 diabetes mellitus; however, it is also a fundamental mechanism for metabolic syndrome and its components, namely, hypertension and hypercholesterolemia.[29,30] In this study, we analyzed the association of IR and SLI using 3 models: adjusting for antidiabetic medication, adjusting for diabetes mellitus, and after the exclusion of diabetes mellitus patients. IR was associated with the presence and severity of SLI in all the 3 models. This implies that IR is a risk factor of SLI, irrespective of diabetes mellitus and other cardiovascular risk factors.

It is still unclear whether the pathophysiology of SLI is different from cortical ischemic stroke and is a point that is currently under debate.[5,7] Nonetheless, SLI can be attributed to 2 main pathological mechanisms: atherosclerosis and endothelial dysfunction.

Atherosclerosis has been observed as a pathological feature of SLI.[31] Early studies including postpartum specimens

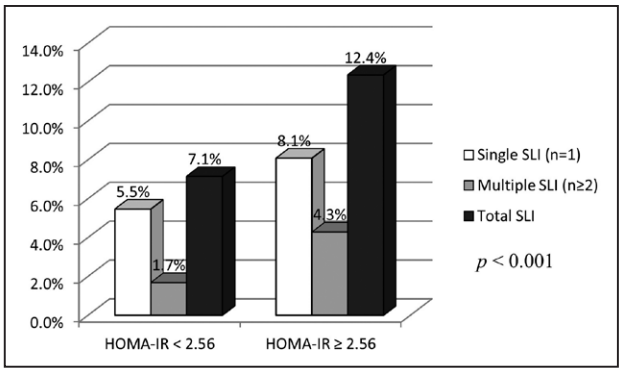

Figure. The relationship between insulin resistance and the number of silent lacunar infarction (SLI) occurrence. HOMA-IR indicates homeostasis model assessment–estimated insulin resistance.

showed focal atheromas and atheromatous stenosis associated with SLI lesions. Also, many typical vascular risk factors that are known to be associated with atherosclerosis contribute to the development of SLI.[32]

Recently, many cellular and molecular studies have provided detailed rationales for the association between IR and atherosclerosis.[29,33] First, IR is associated with elevated levels of inflammatory markers. This proinflammatory condition is also related to atherosclerosis. Second, IR may disturb some signaling pathways, making them proatherogenic. For instance, the mitogen-activated protein kinase signaling pathway is enhanced in IR condition, which may contribute to atherosclerosis with an increase in cell adhesion and interactions. Thus, IR may aggravate atherosclerosis in varied ways, contributing to the development of SLI.

However, it was recently proposed that endothelial dysfunction is also a key process in the development of SLI. This hypothesis is supported by the observation that the arteriolar wall appeared thickened as it passed through the lacunar infarction lesion, not proximal to it.[31] It is regarded that the activation of the cerebral microvascular endothelium might be the primary step in the pathogenesis of SLI, subsequently leading to increased permeability of the blood–brain barrier.[34,35] IR is also suggested to be related to endothelial dysfunction. Both IR and endothelial dysfunction are commonly observed in many cardiovascular diseases.[36,37] The link between IR and endothelial dysfunction is explained by some molecular and cellular mechanisms. IR increases lipolysis and induces proinflammatory cytokines. Such lipotoxicity and inflammation may contribute to endothelial dysfunction, explaining the link between IR and endothelial dysfunction.[36,37]

Thus, IR may lead to the development of SLI, via both endothelial dysfunction and atherosclerosis. In this study, we investigated the association of C-reactive protein, which is one of known inflammatory marker associated with both atherosclerosis[38] and endothelial dysfuntion,[39] with SLI. However, it did not show a significant association with the presence and severity of SLI. Nonetheless, because C-reactive protein is only one nonspecific inflammatory parameter, among numerous atherosclerosis and endothelial dysfunction development-related markers,[40] the hypothesis linking IR-induced atherosclerosis and endothelial dysfunction to SLI development is still valid and should be evaluated in a separate, well-designed trial.

In addition, we assessed the association of IR and the volume of WMH. WMH is strongly associated with the risk of stroke[41]; however, its pathogenesis and risk factors are not well-known.[41] In this study, IR did not show significant association with the volume of WMH. However, aging and hypertension were positively associated with WMH, and BMI showed a negative association. This result implied that WMH has different risk factors from lacunar infarction, which is consistent with a recent study.[12]

This study has some limitations. First, as a cross-sectional study, this study cannot convince the causal relationship between IR and SLI. It is possible that IR is just associated with endothelial dysfunction or atherosclerosis and does not have causal effect on SLI. Second, we estimated IR by the HOMA-IR index, not by the euglycemic hyperinsulinemic clamp method, which is the gold standard for IR measurement. However, the clamp method is cumbersome and unsuitable for large studies. HOMA-IR is a commonly used alternative method in clinical and epidemiological studies. Third, because the cutoff level of HOMA-IR is influenced by race, age, and disease, it is not uniform. We tried to apply the appropriate cutoff level for the participants in this study, by using the HOMA-IR cutoff level from a study with healthy Korean population. In addition, we performed a further analysis using the Japan criteria with a similar ethnic background, which showed the same significant results. Fourth, antidiabetic medication was not assessed by different categories, which could influence IR differently. Fifth, this study does not provide functional or cognitive correlations.

Conclusions

In conclusion, IR was independently associated with both the presence and the severity of SLI. A longitudinal study of the causality and an interventional trial seeing whether IR improvement might lead to prevention of SLI should be followed.

Sources of Funding

This study was supported, in part, by a grant of Hanmi Pharmaceutical Company, Seoul, Republic of Korea (Grant No 06-2015-0810).

Disclosures

None.

References

1. Vermeer SE, Longstreth WT Jr, Koudstaal PJ. Silent brain infarcts: a systematic review. *Lancet Neurol*. 2007;6:611–619. doi: 10.1016/S1474-4422(07)70170-9.
2. Chen Y, Wang A, Tang J, Wei D, Li P, Chen K, et al. Association of white matter integrity and cognitive functions in patients with subcortical silent lacunar infarcts. *Stroke*. 2015;46:1123–1126. doi: 10.1161/STROKEAHA.115.008998.
3. Gupta A, Giambrone AE, Gialdini G, Finn C, Delgado D, Gutierrez J, et al. Silent brain infarction and risk of future stroke: a systematic review and meta-analysis. *Stroke*. 2016;47:719–725. doi: 10.1161/STROKEAHA.115.011889.
4. Wardlaw JM. What causes lacunar stroke? *J Neurol Neurosurg Psychiatry*. 2005;76:617–619. doi: 10.1136/jnnp.2004.039982.
5. Jackson C, Sudlow C. Are lacunar strokes really different? A systematic review of differences in risk factor profiles between lacunar and nonlacunar infarcts. *Stroke*. 2005;36:891–901. doi: 10.1161/01.STR.0000157949.34986.30.

6. Li Y, Liu N, Huang Y, Wei W, Chen F, Zhang W. Risk factors for silent lacunar infarction in patients with transient ischemic attack. *Med Sci Monit*. 2016;22:447–453.
7. Lv P, Jin H, Liu Y, Cui W, Peng Q, Liu R, et al. Comparison of risk factor between lacunar stroke and large artery atherosclerosis stroke: a cross-sectional study in China. *PLoS One*. 2016;11:e0149605. doi: 10.1371/journal.pone.0149605.
8. Kim MH, Moon JS, Park SY, An SA, Kim OJ, Kim NK, et al. Different risk factor profiles between silent brain infarction and symptomatic lacunar infarction. *Eur Neurol*. 2011;65:250–256. doi: 10.1159/000324335.
9. Kwon HM, Kim BJ, Lee SH, Choi SH, Oh BH, Yoon BW. Metabolic syndrome as an independent risk factor of silent brain infarction in healthy people. *Stroke*. 2006;37:466–470. doi: 10.1161/01.STR.0000199081.17935.81.
10. Park K, Yasuda N, Toyonaga S, Tsubosaki E, Nakabayashi H, Shimizu K. Significant associations of metabolic syndrome and its components with silent lacunar infarction in middle aged subjects. *J Neurol Neurosurg Psychiatry*. 2008;79:719–721. doi: 10.1136/jnnp.2007.134809.
11. Grundy SM. Metabolic syndrome update. *Trends Cardiovasc Med*. 2016;26:364–373. doi: 10.1016/j.tcm.2015.10.004.
12. Dearborn JL, Schneider AL, Sharrett AR, Mosley TH, Bezerra DC, Knopman DS, et al. Obesity, insulin resistance, and incident small vessel disease on magnetic resonance imaging: Atherosclerosis Risk in Communities Study. *Stroke*. 2015;46:3131–3136. doi: 10.1161/STROKEAHA.115.010060.
13. Kernan WN, Viscoli CM, Furie KL, Young LH, Inzucchi SE, Gorman M, et al; IRIS Trial Investigators. Pioglitazone after ischemic stroke or transient ischemic attack. *N Engl J Med*. 2016;374:1321–1331. doi: 10.1056/NEJMoa1506930.
14. Howard G, Wagenknecht LE, Kernan WN, Cushman M, Thacker EL, Judd SE, et al. Racial differences in the association of insulin resistance with stroke risk: the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study. *Stroke*. 2014;45:2257–2262. doi: 10.1161/STROKEAHA.114.005306.
15. Rundek T, Gardener H, Xu Q, Goldberg RB, Wright CB, Boden-Albala B, et al. Insulin resistance and risk of ischemic stroke among non-diabetic individuals from the northern Manhattan study. *Arch Neurol*. 2010;67:1195–1200. doi: 10.1001/archneurol.2010.235.
16. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al; National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA*. 2003;289:2560–2572. doi: 10.1001/jama.289.19.2560.
17. Grundy SM, Becker D, Clark LT, Cooper RS, Denke MA, Howard J, et al. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation*. 2002;106:3143.
18. American Diabetes Association. Standards of medical care in diabetes—2015 abridged for primary care providers. *Clin Diabetes*. 2015;33:97–111. doi: 10.2337/diaclin.33.2.97.
19. Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, et al; National Kidney Foundation. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Intern Med*. 2003;139:137–147.
20. World Health Organization. *The Asia-Pacific Perspective: Redefining Obesity and Its Treatment*. 2000. http://www.wpro.who.int/nutrition/documents/docs/Redefiningobesity.pdf.
21. Motamed N, Miresmail SJ, Rabiee B, Keyvani H, Farahani B, Maadi M, et al. Optimal cutoff points for HOMA-IR and QUICKI in the diagnosis of metabolic syndrome and non-alcoholic fatty liver disease: a population based study. *J Diabetes Complications*. 2016;30:269–274. doi: 10.1016/j.jdiacomp.2015.11.019.
22. Shashaj B, Luciano R, Contoli B, Morino GS, Spreghini MR, Rustico C, et al. Reference ranges of HOMA-IR in normal-weight and obese young Caucasians. *Acta Diabetol*. 2016;53:251–260. doi: 10.1007/s00592-015-0782-4.
23. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*. 1985;28:412–419.
24. Park SH, Lee WY, Rhee EJ, Jeon WK, Kim BI, Ryu SH, et al. Relative risks of the metabolic syndrome according to the degree of insulin resistance in apparently healthy Korean adults. *Clin Sci (Lond)*. 2005;108:553–559. doi: 10.1042/CS20040331.
25. Yamada C, Kondo M, Kishimoto N, Shibata T, Nagai Y, Imanishi T, et al. Association between insulin resistance and plasma amino acid profile in non-diabetic Japanese subjects. *J Diabetes Investig*. 2015;6:408–415. doi: 10.1111/jdi.12323.
26. Esteghamati A, Ashraf H, Khalilzadeh O, Zandieh A, Nakhjavani M, Rashidi A, et al. Optimal cut-off of homeostasis model assessment of insulin resistance (HOMA-IR) for the diagnosis of metabolic syndrome: third national surveillance of risk factors of non-communicable diseases in Iran (SuRFNCD-2007). *Nutr Metab (Lond)*. 2010;7:2–8.
27. Rost NS, Rahman RM, Biffi A, Smith EE, Kanakis A, Fitzpatrick K, et al. White matter hyperintensity volume is increased in small vessel stroke subtypes. *Neurology*. 2010;75:1670–1677. doi: 10.1212/WNL.0b013e3181fc279a.
28. Bender R, Grouven U. Ordinal logistic regression in medical research. *J R Coll Physicians Lond*. 1997;31:546–551.
29. Stöhr R, Federici M. Insulin resistance and atherosclerosis: convergence between metabolic pathways and inflammatory nodes. *Biochem J*. 2013;454:1–11. doi: 10.1042/BJ20130121.
30. Brown AE, Walker M. Genetics of insulin resistance and the metabolic syndrome. *Curr Cardiol Rep*. 2016;18:75. doi: 10.1007/s11886-016-0755-4.
31. Wardlaw JM, Smith C, Dichgans M. Mechanisms of sporadic cerebral small vessel disease: insights from neuroimaging. *Lancet Neurol*. 2013;12:483–497. doi: 10.1016/S1474-4422(13)70060-7.
32. Lee SC, Park SJ, Ki HK, Gwon HC, Chung CS, Byun HS, et al. Prevalence and risk factors of silent cerebral infarction in apparently normal adults. *Hypertension*. 2000;36:73–77.
33. Nigro J, Osman N, Dart AM, Little PJ. Insulin resistance and atherosclerosis. *Endocr Rev*. 2006;27:242–259. doi: 10.1210/er.2005-0007.
34. Saji N, Toba K, Sakurai T. Cerebral small vessel disease and arterial stiffness: tsunami effect in the brain? *Pulse (Basel)*. 2016;3:182–189. doi: 10.1159/000443614.
35. Knottnerus IL, Ten Cate H, Lodder J, Kessels F, van Oostenbrugge RJ. Endothelial dysfunction in lacunar stroke: a systematic review. *Cerebrovasc Dis*. 2009;27:519–526. doi: 10.1159/000212672.
36. Janus A, Szahidewicz-Krupska E, Mazur G, Doroszko A. Insulin resistance and endothelial dysfunction constitute a common therapeutic target in cardiometabolic disorders. *Mediators Inflamm*. 2016;2016:3634948. doi: 10.1155/2016/3634948.
37. Kim JA, Montagnani M, Koh KK, Quon MJ. Reciprocal relationships between insulin resistance and endothelial dysfunction: molecular and pathophysiological mechanisms. *Circulation*. 2006;113:1888–1904. doi: 10.1161/CIRCULATIONAHA.105.563213.
38. Syed Ikmal SI, Zaman Huri H, Vethakkan SR, Wan Ahmad WA. Potential biomarkers of insulin resistance and atherosclerosis in type 2 diabetes mellitus patients with coronary artery disease. *Int J Endocrinol*. 2013;2013:698567. doi: 10.1155/2013/698567.
39. Wiseman S, Marlborough F, Doubal F, Webb DJ, Wardlaw J. Blood markers of coagulation, fibrinolysis, endothelial dysfunction and inflammation in lacunar stroke versus non-lacunar stroke and non-stroke: systematic review and meta-analysis. *Cerebrovasc Dis*. 2014;37:64–75. doi: 10.1159/000356789.
40. Di Napoli M, Elkind MS, Godoy DA, Singh P, Papa F, Popa-Wagner A. Role of C-reactive protein in cerebrovascular disease: a critical review. *Expert Rev Cardiovasc Ther*. 2011;9:1565–1584. doi: 10.1586/erc.11.159.
41. Smith EE. Leukoaraiosis and stroke. *Stroke*. 2010;41(10 suppl):S139–S143. doi: 10.1161/STROKEAHA.110.596056.

Insulin Resistance Is a Risk Factor for Silent Lacunar Infarction

Ji Eun Lee, Dong Wook Shin, Jae Moon Yun, Sang Hyuck Kim, You-Seon Nam, BeLong Cho, Jae-Sung Lim, Han-Yeong Jeong, Hyung-Min Kwon and Jin-Ho Park

Stroke. published online November 8, 2016;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0039-2499. Online ISSN: 1524-4628