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Higher Glycated Hemoglobin Level Is Associated with Increased Risk for Ischemic Stroke in Non-Diabetic Korean Male Adults

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Background: The role of glycated hemoglobin (HbA1c) in the prediction of ischemic stroke in non-diabetic subjects is not clear. We performed a study to analyze the role of HbA1c in the risk prediction of ischemic stroke in non-diabetic Korean males adult.
Methods: A total of 307 non-diabetic male patients with ischemic stroke were enrolled, and 253 age-matched control subjects without a history of diabetes, hypertension, or cardiovascular disease were selected from a Health Check-up database. Anthropometric measurement data, fasting glucose level, lipid profile, and HbA1c level were available for all subjects. Associations of the variables and the presence or absence of ischemic stroke were analyzed.
Results: The ischemic stroke patient group had significantly higher HbA1c levels (5.8±0.5% vs. 5.5±0.5%, $P<0.01$) and mean systolic and diastolic blood pressure compared with the control group. Among the variables, smoking, low high density lipoprotein cholesterol, systolic blood pressure, and HbA1c were the significant determinants for ischemic stroke. The highest quartile of HbA1c showed a 9.6-fold increased odds ratio for ischemic stroke compared with the lowest quartile of HbA1c (odds ratio, 9.596; 95% confidence interval, 3.859 to 23.863, $P<0.01$). The proportion of ischemic stroke patients showed a significant trend for increment as the deciles of HbA1c increased (P for trend <0.01).
Conclusion: Higher HbA1c indicated a significantly increased risk for ischemic stroke after adjusting for other confounding variables in non-diabetic Korean adult males. HbA1c might have significance in predicting the risk for ischemic stroke even in the non-diabetic range.

Keywords: Glycated hemoglobin; Koreans; Stroke

INTRODUCTION

Stroke is expected to be the second most important cause of mortality worldwide by 2020. Approximately 60% of the world's total mortality in 2002 was due to stroke, and in the East Asian region, which comprises Southeast Asia and the Western Pacific regions, stroke caused a total 3 million deaths in that year. The rapid socioeconomic changes in these regions during recent years have led to changes in lifestyle and diet that can greatly influence the risk factors for diseases such as stroke [1].

Approximately 30% to 40% of acute ischemic stroke patients present with hyperglycemia at admission either as a result of preexisting diabetes mellitus or acute stress response. Type 2 diabetes, a disease that affects more than 220 million people worldwide, has an alarming number of new cases in the Asian population and holds a 2- to 6-fold increased risk for ischemic

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stroke. Moreover, hyperglycemia is associated with poor outcome in acute ischemic stroke. Thus, in recent years, there has been a growing interest in methods to manage hyperglycemia in acute ischemic stroke [2,3].

Glycated hemoglobin (HbA1c) level reflects the mean glucose control range for the previous 2 to 3 months in patients with or without diabetes mellitus. HbA1c level is widely recommended as the therapeutic guideline for the prevention of cardiovascular complications in patients with diabetes [4]. Recently published clinical practice recommendations from the American Diabetes Association advocate the use of a HbA1c level greater than 6.5% for the diagnosis of diabetes, largely on the basis of the established association between HbA1c level and microvascular complications. Compared with fasting glucose, HbA1c has higher repeatability, can be tested in a non-fasting status, and is a relatively stable marker for glucose level. The disadvantage of the use of HbA1c in the diagnosis of diabetes might be the fact that the measurement of HbA1c level is not standardized, which may result in unreliable values in different laboratories and countries [5].

Despite the recent impending increase in risk for diabetes and ischemic stroke in Asians, and the increasing importance of predictive value of HbA1c in future risk for cardiovascular disease, there are no studies that have investigated the association of ischemic stroke with HbA1c level in Asians. We cross-sectionally analyzed the risk for ischemic stroke according to HbA1c level in Korean male patients admitted due to acute ischemic stroke without a previous history of diabetes.

METHODS

Study subjects

This was a case-controlled study in which ischemic stroke patients were selected from the Soonchunhyang stroke registry database. Among 1,685 patients who were admitted to the Neurology Department of 3 Soonchunhyang University-affiliated Hospitals in Seoul, Bucheon, and Cheonan due to acute ischemic stroke from September 2007 to April 2009, a total of 307 male patients (mean age, 63 years) were selected. All patients had suffered from focal symptoms and had been observed within 1 week of symptom onset and showed relevant lesions on magnetic resonance diffusion-weighted imaging (DWI). Subjects without fasting blood glucose and HbA1c level data were excluded from the study. Patients with a history of diabetes and fasting blood glucose level ≥126 mg/dL were also excluded from the analyses. Only male adult subjects were selected, and patients with cardioembolic ischemic stroke were also excluded from the study. Ischemic stroke subtype was classified according to the Trial of Org 10,172 in Acute Stroke Treatment (TOAST) criteria [6].

A total of 253 age-matched control male subjects without a history of diabetes, hypertension, or cardiovascular disease were selected from the Health Check-up database of Kangbuk Samsung Hospital Health Promotion Center, Seoul, Korea. The purpose of the medical health check-up program is to promote the health of employees through regular health check-ups and early detection of existing diseases. Most of the examinees are employees or family members of various industrial companies all around the country. The employer typically pays the cost of these medical exams, and a considerable proportion of the examinees repeat the exam annually or biannually.

Case-controlled analyses were performed in these two cohorts to assess the risk for ischemic stroke according to HbA1c category (Fig. 1). The Institutional Review Board of Soonchunhyang University Cheonan Hospital approved the protocol and data analysis for this study.

Laboratory measurements

Height and weight were measured in duplicate, and the results were averaged. Body mass index (BMI) was calculated by di-

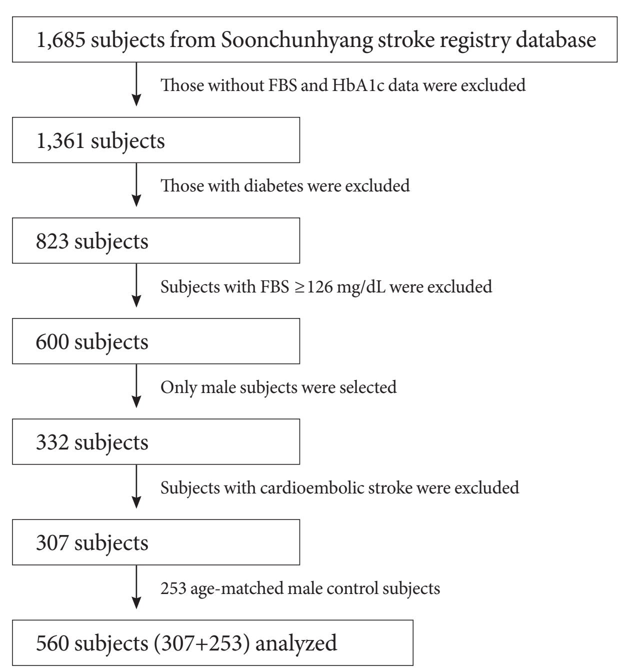

Fig. 1. Selection of study subjects.

viding the weight (kg) by the height (m) squared. All subjects were examined after an overnight fast. The hexokinase method (Advia 1,650 Autoanalyzer; Bayer Diagnostics, Leverkusen, Germany) was used to measure blood glucose level. An enzymatic colorimetric test was used to measure total cholesterol (TC) and triglyceride concentrations. The selective inhibition method was used to measure the level of high density lipoprotein cholesterol (HDL-C), and a homogeneous enzymatic calorimetric test was used to measure the level of low density lipoprotein cholesterol (LDL-C).

HbA1c was measured using an immunoturbidimetric assay with a Cobra Integra 800 automatic analyzer (Roche Diagnostics, Basel, Switzerland) with a reference value of 4.4% to 6.4%. The methodology was aligned with the Diabetes Control and Complications Trial (DCCT) and National Glycohemoglobin Standardization Program (NGSP) standards [7]. The intra-assay coefficient of variation (CV) was 2.3%, and the inter-assay CV was 2.4%, both within NGSP acceptable limits [8].

Subjects were divided into 4 groups according to the quartiles of HbA1c level for the assessment of risk for ischemic stroke: 1st quartile, HbA1c≤5.3%; 2nd quartile, 5.3<HbA1c≤5.6%; 3rd quartile, 5.6<HbA1c≤6.0%; and 4th quartile, HbA1c>6.0%. In addition, subjects were divided into 10 groups according to the decile of HbA1c, and the proportion of the patients with ischemic stroke was assessed according to the HbA1c decile.

Statistical analysis

Data are expressed as the subject number with proportion (%) and mean with standard deviation. Comparison of the mean variables between the ischemic stroke patients and control subjects was performed with Student's *t*-tests. Logistic regression analysis with ischemic stroke as the dependent variable was performed with age, smoking, body mass index, HDL-C, LDL-C, systolic and diastolic blood pressure, and quartile of HbA1c included in the model. The proportion of patients with ischemic stroke was analyzed according to the decile of HbA1c using the chi-square test. Mean values of HbA1c were compared among the groups divided by TOAST classification using a one-way analysis of variance (ANOVA) test. *P* values less than 0.05 were considered statistically significant.

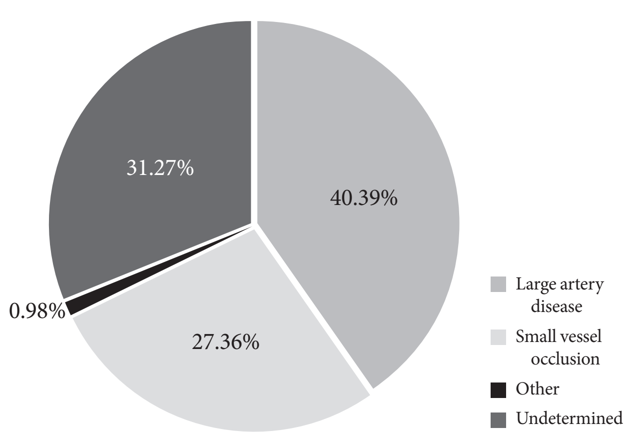

Fig. 2. Distribution of ischemic stroke patients according to TOAST classification. TOAST, Trial of Org 10172 in Acute Stroke Treatment.

RESULTS

General characteristics of the participants are presented in Table 1. According to TOAST classification, 124 patients (40.39%) had large artery disease, 84 (27.36%) had small vessel disease, 96 (31.27%) had undetermined disease, and 3 (0.98%) had other diseases (Fig. 2). Ischemic stroke patients showed a higher mean weight and mean HbA1c level compared to control subjects (Table 1). Mean values for TC and LDL-C were significantly lower in stroke patients, and the mean HDL-C level was sig-

Table 1. Comparison of mean variables between patients with ischemic stroke and control subjects

Variable	Ischemic stroke patients (n=307)	Control subjects (n=253)	*P* value
Age, yr	62.9±13.3	62.3±8.9	0.601
Weight, kg	68.4±16.3	66.1±8.3	0.027
Height, cm	165.3±14.0	167.4±5.6	0.018
BMI, kg/m^2	23.9±2.8	23.5±2.5	0.129
Fasting glucose, mg/dL	100.6±13.8	99.5±10.9	0.306
HbA1c, %	5.8±0.5	5.5±0.5	<0.01
SBP, mm Hg	145.5±24.6	115.7±11.2	<0.01
DBP, mm Hg	88.5±14.5	76.5±7.9	<0.01
TC, mg/dL	179.6±36.9	195.0±35.3	<0.01
Triglyceride, mg/dL	139.6±84.2	132.1±82.6	0.294
HDL-C, mg/dL	45.0±13.0	51.4±12.3	<0.01
LDL-C, mg/dL	106.6±31.9	113.9±27.8	0.004
Smoking, *n* (%)	157 (51.1)	14 (5.5)	<0.01

Values are presented as mean±standard deviation or number (%).
BMI, body mass index; HbA1c, glycated hemoglobin; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol.

Table 2. Logistic regression analysis with ischemic stroke as the dependent variable

Variable	OR	95% CI	*P* value
Age	0.991	0.963-1.019	0.518
Smoking	25.218	10.725-59.294	<0.01
BMI	0.925	0.820-1.043	0.201
HDL-C	0.961	0.936-0.986	0.003
LDL-C	0.992	0.983-1.002	0.108
SBP	1.123	1.088-1.158	<0.01
DBP	1.016	0.971-1.064	0.489
HbA1c <5.3%	1	-	-
5.3< HbA1c≤5.6%	1.450	0.586-3.589	0.422
5.6<HbA1c≤6.0%	4.453	1.903-10.421	0.001
HbA1c>6.0%	9.596	3.859-23.863	<0.01

Adjusted for age, smoking, BMI, HDL-C, LDL-C, SBP, DBP, quartile of HbA1c.
OR, odds ratio; CI, confidence interval; BMI, body mass index; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin.

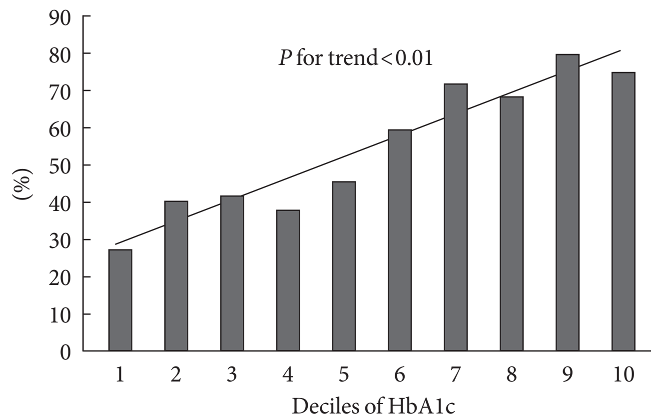

Fig. 3. The proportion of subjects with ischemic stroke according to HbA1c decile in Korean adult males. HbA1c, glycated hemoglobin.

nificantly lower in ischemic stroke subjects compared to control subjects. The mean systolic and diastolic blood pressure values were significantly higher in ischemic stroke patients compared to control subjects, and significantly more subjects in the ischemic stroke group were smokers compared to the control subjects (Table 1).

When a logistic regression analysis was performed with ischemic stroke as the dependent variable, smoking, HDL-C, systolic blood pressure, and increasing HbA1c were the significant predictors for ischemic stroke development (Table 2). Patients who smoked showed a 25-fold increased risk for ischemic stroke. After adjustment for confounding variables, patients in the highest HbA1c quartile showed a nearly 10-fold increased risk for ischemic stroke compared with those in the lowest HbA1c quartile (Table 2).

When the subjects were divided into 10 groups according to decile of HbA1c, the proportion of patients with ischemic stroke showed a significant trend for increment as the decile of HbA1c increased (*P* for trend <0.01, Fig. 3).

When the mean HbA1c values were compared among patients with ischemic stroke subtypes divided by TOAST classification, the mean values of HbA1c for patients with ischemic stroke due to large artery disease, small vessel disease, other disease, and undetermined cause were 5.80±0.46, 5.82±0.58, 4.90±0.46, and 5.79±0.50%, respectively (P=0.024 by one-way ANOVA test).

DISCUSSION

In this cross-sectional, case-controlled study, patients with ischemic stroke showed a significantly increased mean HbA1c level compared with those of the age-matched control subjects. The odds ratio for ischemic stroke increased as the quartile of HbA1c increased from the first to the fourth quartile, and patients in the highest quartile of HbA1c showed a nearly 10-fold increased risk for ischemic stroke compared with patients in the lowest quartile. The proportion of patients with ischemic stroke showed a significantly increasing trend as the HbA1c decile increased from the first to the tenth decile, supporting the conclusion that higher HbA1c is associated with increased risk for ischemic stroke even in the non-diabetic HbA1c range. These results suggest a predictive value of increasing HbA1c for ischemic stroke risk in non-diabetic Korean male subjects.

The International Federation of Clinical Chemistry newly defines HbA1c as hemoglobin that is irreversibly glycated at one or both of the β-chain N-terminal valines, and it does not exclude hemoglobin that is additionally glycated at other sites on the α or β chains [9]. HbA1c could reflect universal tissue protein glycation and might be a much better index of the overall biological effects of glucose above and beyond its predictive value for the 3-month averages of circulating glucose level [10]. Although there are many studies that report the utility of HbA1c in predicting cardiovascular disease and diabetes, there are few that investigate the usefulness of HbA1c as a predictor of ischemic stroke.

Prior studies have demonstrated variable results with regard to an association of HbA1c with cardiovascular disease. In the Rancho Bernardo cohort of 1,239 older non-diabetic adults, baseline HbA1c, but not fasting or post-challenge glucose, predicted cardiovascular mortality in women but not in men [11]. In the EPIC-Norfolk study, a 1% increment in HbA1c was associated with a 21% increase in cardiovascular risk after multivariable adjustment in both men and women. However, when subjects with prior diabetes and cardiovascular disease were excluded, this association was diminished and not statistically significant [12]. In the Hoorn Study, which also presented categorical analyses with and without adjustment for traditional risk factors, the age-adjusted risk in the highest vs. lowest category (≥6.5% vs. <5.2%) was 3.8. However, after additional adjustment for gender, hypertension, dyslipidemia, and smoking, this effect was attenuated and no longer statistically significant [13]. In a nested case-controlled study in the Women's Health Study cohort, HbA1c level was not predictive of cardiovascular events after adjustment for confounding effects of correlated cardiovascular risk factors [14]. In a previous study performed in 26,563 U.S. female health professionals with a follow-up period of 10 years, HbA1c failed to predict cardiovascular disease in non-diabetic women [15].

On the other hand, a previous study using a case-cohort design found associations of HbA1c with coronary heart disease and stroke in a subgroup of the ARIC population with low fasting glucose levels (at two time points) and low HbA1c values among persons with diabetes [16,17]. In a very recent study from a community-based population of non-diabetic adults followed-up for 14 years, HbA1c was significantly associated with a future risk for diabetes, cardiovascular disease, and death from any cause as compared with fasting glucose. In this study, subjects with a baseline level of HbA1c between 5.0% and 5.5% were compared with subjects having higher HbA1c values, and their risk for ischemic stroke linearly increased as the baseline level of HbA1c increased. These significances were more prominent in HbA1c values compared with fasting glucose. Despite significant differences between blacks and whites in HbA1c value at baseline, race did not modify the association among HbA1c value, cardiovascular outcome and death in this population [18]. There have also been a few studies performed in non-diabetic Korean adults reporting the association between the risks for coronary artery disease or metabolic syndrome [19,20], but no studies were performed on the association of HbA1c and the risk for ischemic stroke in Koreans.

We analyzed the risk for ischemic stroke only in male adults because we wanted to determine if there were any gender differences considering that HbA1c failed to predict cardiovascular disease in non-diabetic women [15]. We also failed to show the usefulness of HbA1c as a predictor of ischemic stroke in non-diabetic Korean women. This result might be due to a lack of consideration for hormonal change or hormonal replacement therapy in postmenopausal women. Recent studies reported that sex hormone and sex hormone-binding globulin, in addition to HbA1c, are associated with a risk of type 2 diabetes [21,22]. Because the average age of women in our study was in the sixties, and they were mostly postmenopausal women having severe hormonal change, it might be difficult to show the association of HbA1c as a predictor of ischemic stroke.

Our study has several limitations. First, it was a cross-sectional study such that a definite relationship between HbA1c and ischemic stroke cannot be assumed. Further research in a more diverse ethnic group must be conducted to clarify this relationship. Second, this study might cause controversy about the representativeness of stroke patients. However, our objects of study were stroke patients from 3 different regions representing a large city, a medium-sized city, and a rural area, respectively. The characteristics of stroke patients in this study were similar to those of nationwide Korean Stroke Registry data, so the groups of patients in this study could be representative of stroke patients in Korea to some extent. Third, according to the classification of ischemic stroke subtype in this study, the number of patients with cardioembolic ischemic stroke was smaller than usual, which might be explained because studies for cardiac source of ischemic stroke were insufficient. Fourth, the mean values for TC and LDL-C were significantly lower in stroke patients, and these differences might be assumed to be due to the higher percentage of lipid-lowering medications used in this study population. Fifth, the diagnosis of type 2 diabetes was only based on the levels of fasting glucose and HbA1c without a glucose challenge test. Therefore, there is still the possibility that subjects with overt diabetes could have been included in this study, although recent guidelines recommend that fasting glucose and HbA1c levels are sufficient to diagnose diabetes [5]. In spite of these limitations, the results of this study are meaningful in that this study was the first to report the association of increasing HbA1c with risk for ischemic stroke in non-diabetic Korean adults.

In conclusion, higher HbA1c indicated a significantly increased risk for ischemic stroke after adjusting for other confounding variables in non-diabetic Korean adult males. In addition, HbA1c might have significance in predicting the risk for ischemic stroke even in the non-diabetic range. Therefore, efforts to maintain glucose level within the normal range in subjects with high cardiovascular risk are important. These data support the need for a prospective study examining levels of HbA1c and future ischemic stroke in Korean subjects.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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