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ORIGINAL RESEARCH

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Sex differences in the association between fasting glucose and ischemic stroke incidence in people without diabetes: a 19-year prospective cohort study in Korea

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Abstract

This study aimed to determine whether high fasting blood glucose (FBG) levels are a risk factor for ischemic stroke (IS) in the population without diabetes and conduct an interaction analysis to explore the potential differential effects of FBG levels and sex on IS risk. We used data from the Genome and Epidemiology Study (KoGES). The primary exposure was serum FBG obtained at the first interview. The main outcome was the occurrence of IS in the biennial follow-up surveys. Cox proportional regression analysis was performed to estimate the effects of high FBG on IS incidence. We performed an interaction analysis to examine the effect of FBG and sex interaction on the incidence of IS. Over the 18-year follow-up period, which included 5682 participants, 333 cases of newly diagnosed IS were recorded, equivalent to 5.5 cases per 1000 person-years. Elevated FBG levels did not show a significant impact on IS incidence, with an adjusted hazard ratio (aHR) of 1.06 (95% confidence interval (CI): 0.89–1.26). However, in the interaction analysis, elevated FBG was linked to a higher IS risk in females (aHR: 1.40; 95% CI: 1.03–1.92), while no statistically significant association was observed in males (aHR: 1.07; 95% CI: 0.87–1.48). In the population without diabetes, high FBG ($\geq$100 mg/dL) was associated with an increased risk of IS only in females. This conclusion underscores the need for sex-specific strategies in managing and mitigating the risk of IS associated with high FBG. Even in the absence of diabetes, carefully monitoring and managing high FBG are crucial.

Keywords

Fasting glucose; Stroke; Sex; Diabetes

1. Introduction

Stroke was responsible for 11.6% of all deaths globally, making it the second leading cause of death in 2019 [1]. Ischemic stroke (IS), the most common type, accounted for 62.4% of stroke cases worldwide that year [1]. IS causes neurological death and long-term disability in adults, imposing significant health and economic burdens [2, 3]. Worldwide, 77.19 million people experienced IS in 2019, resulting in 63.48 million disability-adjusted life years (DALYs) lost and 3.29 million deaths [1]. From 1990 to 2019, the age-standardized rates of IS incidence, death and DALYs decreased in both sexes [4].

IS is traditionally linked to various risk factors, many of which are connected to unhealthy lifestyles, such as smoking, obesity and lack of physical activity. Additionally, genetic predisposition and comorbidities, particularly chronic ones, play a significant role. One of the most notable examples is type 2 diabetes mellitus (T2DM). Elevated fasting blood glucose (FBG), indicative of poor glucose metabolism and diabetes management, is linked to a higher risk of cardiovascular diseases, including stroke, although the relationship might be unclear [5–7].

Emerging evidence suggests that the impact of elevated FBG levels and T2DM on IS risk may differ between sexes [8]. Studies showed that women with diabetes are at a disproportionately higher risk of cardiovascular diseases, including IS, compared to men [9]. This disparity may be explained by several factors, including hormonal differences, variations in fat distribution and differences in the prevalence of other risk factors such as hypertension and dyslipidemia between men and women [10, 11]. Additionally, women with diabetes tend to have poorer glycemic control and a higher likelihood of developing complications compared to males [12, 13]. These sex-specific differences in the biological and clinical manifestations of diabetes could influence the risk and outcomes of IS [13]. Consequently, understanding the relationship of FBG with sex and its related influence on stroke incidence is crucial for developing tailored prevention and treatment strategies. Despite these insights, research specifically focusing on sex differences in the relationship between FBG and IS risk is lacking, particularly long-term cohort studies.

In our study, we hypothesized that there is an association

between habitual FBG and the risk of IS. Additionally, similar to how T2DM differently impacts IS risk based on sex, the association between FBG and IS risk might also vary by sex. This study aimed to determine whether high FBG is a risk factor for IS and conduct an interaction analysis to explore the potential differential effects of FBG and sex on IS risk among patients without diabetes.

2. Methods

2.1 Study design and data sources

For this research, the data were obtained from the Korean Genome and Epidemiology Study (KoGES; 6635-302), overseen by the Korea Disease Control and Prevention Agency's National Institute of Health. Established in 2001, KoGES initiated two independent longitudinal cohort studies in different regions: Ansung, a rural region with an approximate population of 176,000 in 2010, and Ansan, an urban region with around 715,000 residents in the same year. Both cohorts comprised individuals aged 40 to 69 years from the Korean population, representing both sexes and similar ethnic backgrounds. Details regarding sampling methods and selection criteria were published in prior studies. From 2001 to 2002, a total of 7129 eligible participants were identified in Ansung, and 10,957 in Ansan. Of these, 5018 participants (2239 men and 2779 women) in Ansung and 5020 participants (2523 men and 2497 women) in Ansan completed the initial health assessments. Follow-up evaluations of these cohorts were conducted regularly, extending up to the 9th cycle in 2019–2020. Interviewers adhered to a standardized protocol, undergoing retraining biennially, while monitoring included site visits every two years.

2.2 Study population and definition of stroke

Our analysis was centered on data obtained from the 2001–2002 cohort, where serum fasting blood glucose (FBG), the primary exposure variable, was measured. An abnormal FBG level was defined as a fasting glucose concentration exceeding 100 mg/dL, consistent with the definition by the American Diabetes Association (ADA) [14].

Participants with physician-confirmed diagnoses of ischemic stroke (IS) or diabetes mellitus (DM) at the baseline survey were excluded. IS cases were identified through self-reports during the 2003–2004 follow-up cycle. Those who reported an IS diagnosis after this cycle were categorized as IS cases for subsequent analyses.

2.3 Variables and measurements

Information was collected on participants' demographics (including age, sex, marital status, education level and socioeconomic status measured by household income) and comorbid conditions (such as hypertension and dyslipidemia), and lifestyle factors (body mass index, smoking status, alcohol consumption and physical activity).

2.4 Statistical analysis

Baseline characteristics of the participants, stratified by normal and high serum FBG levels, were described using summary statistics. Continuous variables were analyzed using the Wilcoxon rank-sum test, while categorical variables were compared with the Chi-square test. The crude incidence of IS over 18 years (2002–2020) was calculated as the number of events per 1000 person-years, stratified by FBG levels and sex. Cox-proportional hazard regression models with fixed covariates were employed to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for cumulative IS incidence over 18 years, based on FBG and sex. The interaction between FBG and sex was analyzed using a multivariate logistic regression model to evaluate the varying effects of FBG changes on IS outcomes by sex. Multicollinearity among covariates was examined within the regression model. Statistical analyses were performed using SAS software (version 9.4; SAS Institute Inc., Cary, NC, USA).

3. Results

3.1 Demographic findings

During the 18-year follow-up, we documented 333 cases of new-onset IS (5.5 cases per 1000 person-years). Table 1 presents the participants' characteristics according to serum FBG level. In the group with high FBG (>100 mg/dL), hypertension incidence was significantly higher compared to the normal FBG group (5.8% *vs.* 4.0%, $p < 0.01$). Additionally, overweight (Body mass index, BMI ≥25) prevalence was significantly higher in the high FBG group. However, there was no significant difference in IS incidence between the two groups. Table 2 shows the participants' characteristics by sex. The male group had a significantly higher proportion of individuals with high FBG (26.7% *vs.* 13.4%) compared to the female group. However, there was no significant difference in IS incidence between the groups.

3.2 Main outcomes

The normal FBG group experienced 269 IS cases, corresponding to an incidence rate of 5.54 per 1000 person-years. In comparison, the high FBG group recorded 64 IS cases, with an incidence rate of 5.43 per 1000 person-years. To assess the influence of exposure variables on IS incidence, a Cox proportional logistic regression analysis was performed, adjusting for all potential confounding variables. After adjustment, high FBG was not found to significantly increase IS incidence (aHR: 1.06; 95% CI: 0.89–1.26). Additionally, no significant difference in IS risk was observed between females and males (aHR: 0.94; 95% CI: 0.70–1.28; Table 3).

3.3 Interaction analysis

In the analysis of interaction effects evaluating the combined influence of FBG and sex on IS incidence, high FBG was linked to a higher IS risk exclusively in females, with an aHR of 1.40 (95% CI: 1.03–1.92). In contrast, no statistically significant association was observed in males, with an aHR of 1.07 (95% CI: 0.87–1.48; p for interaction < 0.001; Table 4).

TABLE 1. Demographic findings of the study population according to serum fasting glucose.

Variables	All	Fasting blood glucose level		*p*-value
	N (%)	Normal (70–100 mg/dL)	High (>100 mg/dL)	
All	5682 (100.0)	4568 (100.0)	1114 (100.0)	
Age, yr, mean (SD)	51.6 (8.6)	51.6 (8.5)	51.7 (8.2)	
Sex, female	3030 (53.3)	2624 (57.4)	406 (36.4)	<0.001
Married, yes	5045 (88.8)	4057 (88.8)	988 (88.7)	0.915
Years of education (≥9)	1582 (27.8)	1251 (27.4)	331 (29.7)	0.125
SES, low	2379 (41.9)	1881 (41.2)	498 (44.7)	0.034
Comorbidity				
Hypertension	250 (4.4)	185 (4.0)	65 (5.8)	<0.001
Dyslipidemia	82 (1.4)	62 (1.4)	20 (1.8)	0.277
BMI				
<18.5 (underweight)	110 (1.9)	96 (2.1)	14 (1.3)	
18.5–24.9 (normal weight)	3170 (55.8)	2686 (58.8)	484 (43.4)	<0.001
>25.0 (overweight)	2402 (42.3)	1786 (39.1)	616 (55.3)	
Lifestyle factors				
Alcohol, yes	2665 (46.9)	2022 (44.3)	643 (57.7)	<0.001
Smoking				
Current	948 (16.7)	713 (15.6)	235 (21.1)	
Former smoker	899 (15.8)	638 (14.0)	261 (23.4)	<0.001
Never smoker	3835 (67.5)	3217 (70.4)	618 (55.5)	
Physical activity, vigorous	2196 (38.6)	1739 (38.1)	457 (41.0)	0.073
Total stroke cases	333 (5.9)	269 (5.9)	64 (5.7)	0.852

yr, year; SD, standard deviation; SES, socioeconomic status; BMI, body mass index.

TABLE 2. Demographic findings of the study population according to sex.

Variables	All	Sex		*p*-value
	N (%)	Male	Female	
All	5563 (100.0)	2591 (100.0)	2972 (100.0)	
Fasting blood glucose, high	1090 (19.6)	692 (26.7)	398 (13.4)	<0.001
Age, yr, mean (SD)	51.6 (8.6)	51.2 (8.4)	51.8 (8.7)	0.041
Married, yes	4949 (89.0)	2496 (96.3)	2453 (82.5)	<0.001
Years of education (≥9)	1535 (27.6)	454 (17.5)	1081 (36.4)	<0.001
SES, low	2308 (41.5)	889 (34.3)	1419 (47.7)	<0.001
Comorbidity				
Hypertension	244 (4.4)	126 (4.9)	118 (4.0)	0.101
Dyslipidemia	82 (1.5)	32 (1.2)	50 (1.7)	0.174
BMI				
<18.5 (underweight)	108 (1.9)	67 (2.6)	41 (1.4)	
18.5–24.9 (normal weight)	3104 (55.8)	1510 (58.3)	1594 (53.6)	<0.001
>25.0 (overweight)	2351 (42.3)	1014 (39.1)	1337 (45.0)	
Lifestyle factors				
Alcohol, yes	2621 (47.1)	1,856 (71.6)	765 (25.7)	<0.001
Smoking				
Current	923 (16.6)	875 (33.8)	48 (1.6)	
Former smoker	878 (15.8)	860 (33.2)	18 (0.6)	<0.001
Never smoker	3762 (67.6)	856 (33.0)	2906 (97.8)	
Physical activity, vigorous	2157 (38.8)	1073 (41.4)	1084 (36.5)	<0.001
Total stroke cases	273 (4.9)	128 (4.9)	145 (4.9)	0.921

SD, standard deviation; SES, socioeconomic status; BMI, body mass index.

TABLE 3. Cox proportional logistic regression analysis for study outcome.

Potential risk factors	Numbers at risk	Stroke events	Person-years	Incidence rate per 1000 PYS	Model 1	Model 2	Model 3
					aHR (95% CI)	aHR (95% CI)	aHR (95% CI)
Fasting glucose level							
Normal	4568	269	48,536.6	5.54	1.00 (reference)	1.00 (reference)	1.00 (reference)
High	1114	64	11,782.7	5.43	1.07 (0.90–1.28)	1.04 (0.88–1.24)	1.06 (0.89–1.26)
Sex							
Male	3001	193	31,139.2	6.20	1.00 (reference)	1.00 (reference)	1.00 (reference)
Female	3382	212	35,993.2	5.89	0.95 (0.78–1.16)	0.95 (0.78–1.16)	0.94 (0.70–1.28)

PYS, person-years; aHR, adjusted hazard ratio; CI, confidence interval.
Model 1: adjusted for age and sex.
Model 2: Model 1 plus hypertension and dyslipidemia.
Model 3: Model 2 plus body mass index, alcohol drinking, smoking and physical activity.

TABLE 4. Interaction analysis between fasting glucose level and sex on study outcome.

	Fasting glucose level		
	Normal	Higher	*p* for interaction
		aHR (95% CI)	<0.001
Male	ref.	1.07 (0.87–1.48)	
N	125	29	
Female	ref.	1.40 (1.03–1.92)	
N	144	35	

aHR, adjusted hazard ratio; CI, confidence interval; N, number.

4. Discussion

Our study revealed significant sex differences in the association between FBG levels and IS risk in the population without diabetes. Over the 18-year follow-up, while high FBG was not associated with an increased risk of IS in the overall population, a notable divergence emerged when the data were stratified by sex. Specifically, high FBG significantly increased the risk of IS in females, but not in males, suggesting a potentially critical sex-specific pathway related to glucose metabolism in the pathophysiology of IS. The significance of these findings lies in the need for sex-specific preventive strategies and interventions in managing FBG to mitigate the risk of IS, particularly in women. Thus, these results underscore the importance of personalized medical approaches and highlight the necessity for further research to understand the underlying mechanisms driving this sex-specific association in individuals without diabetes.

DM is the most common endocrine disorder affecting nearly 6% of the global population and posing a significant public health challenge in all countries [15]. It is characterized by chronic hyperglycemia, affecting glucose, lipid and protein metabolism [16]. DM is a major cause of renal failure, coronary heart disease, non-traumatic lower limb amputations and visual impairment [17–20]. DM and IS frequently co-occur, with DM being an important risk factor for IS. Numerous studies analyzed the association between these two conditions [21–23]. Additionally, research indicates that the association between DM and IS can be influenced by sex, suggesting potential differences in risk profiles between men and women. The Framingham study found that men with DM had a 2.5-fold increased incidence of IS, while women with DM had a 3.6-fold increased incidence compared to their counterparts without diabetes [24]. In Italy, a multicenter cohort study recorded 296 stroke events over a 4-year follow-up among 14,432 participants. The age-standardized incidence of stroke (per 1000 person-years) in individuals without a history of cardiovascular disease was 5.5 (95% CI, 4.2–6.8) in men and 6.3 (95% CI, 4.5–8.2) in women. For those with a history of cardiovascular disease, the incidence rates were 13.7 (95% CI, 7.5–19.8) in men and 10.8 (95% CI, 7.3–14.4) in women [25]. Moreover, it is well-documented that patients with cerebral ischemia and diabetes mellitus have a higher risk of stroke recurrence compared to those without diabetes. This heightened risk is particularly concerning given the interaction between chronic hyperglycemia and vascular health. Persistent hyperglycemia exacerbates vascular damage through mechanisms such as endothelial dysfunction, inflammation and accelerated atherosclerosis, all of which contribute to increased stroke recurrence and worse prognosis in individuals with DM and IS [26].

A study reported that the frequency of hyperglycemia in patients without diabetes presenting with acute stroke was high, with 21.33% of patients experiencing elevated blood glucose levels [27]. However, studies analyzing the associa-

tion between elevated FBG and IS risk in individuals without diabetes are limited. Unlike previous studies, our research did not find a significant association between elevated FBG levels and the risk of IS in individuals without diabetes.

However, elevated FBG was significantly associated with the risk of IS in females in our study. Possible explanations for this finding include hormonal differences. Specifically, the hormonal environment in females, particularly the presence of estrogen, may interact with glucose metabolism, exacerbating the effects of elevated FBG on vascular health [28]. Estrogen has both protective and adverse effects on the cardiovascular system, and its interaction with high blood glucose could increase the risk of IS in women [29, 30]. Additionally, differences in fat distribution and metabolism might play a role, as females typically have a higher percentage of body fat compared to males, and this fat is often distributed in ways that can influence metabolic health [31]. Visceral fat, which is more prevalent in females, is closely linked to insulin resistance and hyperglycemia, potentially increasing the risk of IS when FBG is elevated [32]. Furthermore, previous studies have shown that female sex is a demographic factor associated with worse outcomes and higher recurrence risk in patients with cerebral ischemia [33]. Finally, genetic and epigenetic factors might contribute due to possible genetic or epigenetic differences between males and females influencing how elevated FBG impacts stroke risk [34, 35]. Certain genes related to glucose metabolism and vascular health might be expressed differently in females, leading to a higher susceptibility to the effects of hyperglycemia on the risk of IS.

Our study has several limitations to consider. First, while the data were sourced from the KoGES dataset, potential biases related to age groups, regions, or specific subsets could affect the generalizability of our findings, limiting their applicability to the broader Korean population. Second, the use of self-reported data from KoGES, including medical history and health-related behaviors, may introduce recall or reporting biases. Additionally, external variables not captured in the KoGES dataset might have influenced the results. Third, the dataset used may not fully account for recent advancements in medical research, societal changes or technological progress. Furthermore, the study's statistical power may be insufficient to detect subtle differences or outcomes in scenarios with limited cases, which should be taken into account when interpreting the findings. Fourth, the KoGES dataset lacked detailed information on ischemic stroke subtypes (*e.g.*, lacunar versus non-lacunar strokes) and the anatomical territories of cerebral ischemic strokes (*e.g.*, middle cerebral artery versus posterior cerebral artery), which may influence the distribution of risk factors, stroke severity and clinical outcomes. Lastly, as this study was not a randomized controlled trial, uncontrolled confounding factors could have affected the observed associations. These limitations highlight the need for caution when interpreting and generalizing the study's conclusions.

5. Conclusions

Our study found that elevated FBG was significantly associated with an increased risk of IS in females, suggesting that sex-specific strategies may be necessary to effectively manage and mitigate the risk of IS associated with high FBG. Further research is needed to fully understand the underlying mechanisms driving this sex-specific association. For health policymakers, these results highlight the importance of developing targeted preventive strategies and interventions considering sex differences in glucose metabolism and stroke risk. Implementing such tailored approaches could improve health outcomes and reduce the incidence of IS, particularly in women. Moreover, future research should explore the association between fasting glucose levels and the risk of lacunar versus non-lacunar infarcts among adults without diabetes, focusing on potential sex differences. This line of inquiry is essential because the pathophysiology, prognosis, and clinical features of lacunar strokes differ from other types of acute ischemic cerebrovascular diseases. Investigating these differences could provide deeper insights into the mechanisms of stroke development and support the development of more precise and individualized prevention strategies.

AVAILABILITY OF DATA AND MATERIALS

Data in this study were from the Korean Genome and Epidemiology Study (KoGES; 6635-302), National Institute of Health, Korea Disease Control and Prevention Agency, Republic of Korea.

AUTHOR CONTRIBUTIONS

EJ, HYK and HHR—conceptualization; data curation; formal analysis, supervision; investigation, software, writing original draft, writing review and editing. EJ, UCJ and YSC—methodology. All authors have read and agreed to the published version of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study protocol was reviewed and approved by the Institutional Review Board of Chonnam National University Hospital (CNUH-2018-297). The requirement for informed consent from patients was exempted by Chonnam National University Hospital because the study was a retrospective analysis of existing data.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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