RELATIONSHIP BETWEEN HEMOGLOBIN A1c AND ISCHEMIC STROKE AMONG PATIENTS WITH TYPE-2 DIABETES

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Abstract. Ischemic stroke (IS) is a major cause of morbidity and mortality among patients with diabetes mellitus. In this study we aimed to determine the association between hemoglobin A1c (HBA1c) levels and the IS occurrence among Thai patients with diabetes mellitus type 2 (DM2) in order to reduce the risk for stroke among this group of patients. A hospital based case-control study was conducted among subjects with DM2 who attended the Bhuddasothorn Hospital, Chachoengsao, Thailand with 100 cases and 300 controls during 2013-2016. Cases were defined as patients with DM2 who had an IS and diagnosed by neurologists and computer tomography scan (CT scan) during the study period. Controls were patients with DM2 who did not have IS. Cases (n=100) and controls (n=300) were matched by gender, age (±5 years), residential area, and length of time attending the study hospital. Data were collected using questionnaire comprising demographic characteristics, and medical data. The collected data were analyzed using descriptive statistics and analytic statistics. The mean [±standard deviation (SD)] age of subjects was 66.9 (±11.1) years. Sixty-eight percent of subjects were females. The mean (±SD) HBA1c levels among cases was 9.10 (±2.11)% and among controls was 7.52 (±1.48)%. Multivariable conditional logistic regression was applied to estimate the effect of HBA1c on IS among DM2, revealed a HBA1c of 8-8.9 % and higher increased the risk of IS by a factor of 7.9 and 10.9 times, respectively (OR=7.9, 95%CI: 3.0-20.9; OR=10.9, 95%CI: 4.3-27.9). In summary, we found a significant positive association between HBA1c level and IS. A stroke surveillance system among patients with DM2 should be conducted in cooperation with knowledge sharing regarding glycemic control and stroke prevention as an essential measure to prevent developing IS risk.

Keywords: HBA1c, ischemic stroke, type-2 diabetes

INTRODUCTION

Cerebrovascular disease is primarily comprised of ischemic stroke (IS) and hemorrhagic stroke. Stroke is the second leading cause of death worldwide (Strong *et al*, 2007; Johnston *et al*, 2009). The number

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of strokes per year worldwide is estimated to increase from 38 million in 1990 to 61 million in 2020 (Mackay and Mensah, 2004). In 2010 the Global Burden of Disease, Injuries, and Risk Factors Study (GBD 2010) reported there were an estimated 16.9 million new stroke cases worldwide (Feigin and Krishnamurthi, 2016); most was IS (11.6 million cases) and they resulted in 2.8 million deaths (Bennet, 2012; Murray *et al*, 2012; Feigin *et al*, 2014). The GBD estimates IS by 2020 will account for an estimated 12 million deaths and 200 million disability-adjusted life years (DALYS) lost (Feigin and Krishnamurthi, 2016). In Thailand, stroke is a major health cause of morbidity and mortality in the elderly (Bureau of Policy and Strategies, 2016a). The Thai Ministry of Public Health estimates there are more than 50,000 stroke deaths per year in Thailand (Bureau of Policy and Strategies, 2010; Bureau of Policy and Strategies, 2016b).

Causes of IS are multifactorial. Hyperglycemia is associated with greater risk for IS in western countries (Dhamasaroja, 2008; Hanchaiphiboolkul *et al*, 2014; Nilanont *et al*, 2014; Suwanwela, 2014). In Thailand, quite a few studies have reported this association among DM2. The aim of this study was to determine the association between HbA1c level and IS among patients with diabetes mellitus type 2 (DM2) in order to reduce the risk for stroke among this group of patients.

Variable definitions

Ischemic stroke cases in our study were found by searching the hospital distribution for the International Classification of Diseases, 10th revision (ICD-10) code of I63.

In our study, we used the hemoglobin A1c (HBA1c) level to better reflect level of diabetes control in our study subjects (WHO, 2001).

MATERIALS AND METHODS

Study design, sample size and sampling technique

This was a hospital based case-control study: we conducted it among patients with diabetes mellitus type 2 (DM2) at the Bhuddasothorn Hospital, Chachoengsao, Thailand during 2013-2016. Cases were those who had an IS diagnosed by neurologists and computer tomography scan (CT scan) during the study period and controls were those who did not. Inclusion criteria for cases were DM2 patients with IS, Thais and aged <80 years. Exclusion criteria for cases were those having congenital heart disease with a history of chronic diseases, cancer, tumor, and stroke caused by injury from accident or operation, and having no records of being treated for DM. Inclusion criteria for controls were DM2 without stroke and were being listed on the diabetes registry of the health care network in Chachoengsao Province and lived in the same area with the cases. While exclusion criteria for controls were having a history of transient ischemic attack (TIA) and cardiovascular disease.

A total of 100 IS cases and 300 controls were included in the study. Of the 400 participants, cases and controls were matched by age (±5 years), residential area and the length of time they have been attending the study hospital. The medical records of cases and controls were reviewed. The minimum sample sizes for cases and controls were calculated using the formula by Dupont (1988), where P_0(0.04) and P_1 (0.138) were the proportions of exposure in controls and cases (Sacco *et al*, 1994); $Z_{\alpha/2} = 1.96$ at $\alpha = 0.05$; $Z_{\beta} = 0.84$ at $\beta = 0.20$. The minimum sample size for cases and controls were determined to be 91 cases and 273 controls. Total samples were 100 cases and 300 controls for our study. The

cases and controls data were obtained by reviewing the previous 3 years for exposed factors.

Statistical analyses

Data were analyzed using the statistical software, STATA, version 12 (Stata Corporation, College Station, TX). Data were tabulated using descriptive statistics, univariable analysis and multivariable analysis. Categorical variables were given as frequencies, percentages, crude odds ratios, 95% confidence intervals (CI) for OR and *p*-value. Statistical descriptions were expressed as means, minimums and maximums, standard deviations (SD), frequencies, and percentages. Univariable conditional logistic regression analysis was performed to evaluate association between categorical variables and IS. Adjusted odds ratios and 95% CI for OR were calculated from multivariable conditional logistic regression analysis to examine associations between HbA1c levels and IS, adjusting for potential confounding factors. A two-sided *p*-value <0.05 was considered statistically significant.

Ethical considerations

Our study was approved by the Ethics Committee for Research in Human Subjects, Faculty of Public Health, Mahidol University (171/2557), the Ethics Committee for Research in Human Subjects, Chachoengsao Public Health Office (PH_CCO_REC 004/58), and the Ethics Committee for research, Buddasothorn Hospital (BSH-IRB 005/2558). Informed consent was obtained from each participant prior to inclusion in the study.

RESULTS

Demographic characteristics of study subjects

A total of 100 cases and 300 controls were included in the study. The mean age of study subjects was 67 years (Table 1). Forty-three percent of cases and 43.3% of controls were aged ≥70 years. Sixty-eight percent of subjects were females. Sixty-eight percent of cases and 63.7% of controls had DM2 for 5-10 years. None of the demographic characteristics were significantly different between cases and controls (Table 1).

Factors associated with ischemic stroke

On univariable conditional logistic regression analysis, factors significantly associated with IS were: presence of dyslipidemia, presence of atrial fibrillation, a diastolic blood pressure ≥90 mmHg, a systolic blood pressure ≥140 mmHg, a history of cardiovascular disease, a fasting plasma glucose level ≥126 mg/dl, a serum creatinine level ≥1 mg/dl and the presence of microvascular complications due to DM2 (Table 2). On multivariable conditional logistic regression analysis, a HBA1c level ≥8% was significantly associated with IS. The higher the HbA1c level the greater the odds of having an IS [for HBA1c 8-8.9%: adjusted odds ratios (OR_{adj})=7.9; 95% confidence interval (95%CI):3.0-20.9; $p<0.001$]. For HBA1c≥9%:OR_{adj}=10.9; 95%CI:4.3-27.9; $p<0.001$) (Table 3).

DISCUSSION

In our study, of subjects with DM2, multivariable analyses showed a significant association between HBA1c level and IS, similar to the findings of several previous studies (Najarian *et al*, 2006; Air and Kissela, 2007; Banerjee *et al*, 2012) but in contrast to the findings of other studies (UK Prospective Diabetes Study Group, 1998; Gerstein *et al*, 2008; Holman *et al*, 2008; Patel *et al*, 2008). The pathophysiology of how hyperglycemia is associated with IS could be because elevated glucose

Table 1
General characteristics of study subjects.

Characteristics	Cases (*n*=100) *n* (%)	Controls (*n*=300) *n* (%)	*p*-valuea
Ages in years			1.000
< 50	7 (7.0)	21 (7.0)	
50-59	21 (21.0)	62 (20.7)	
60-69	29 (29.0)	87 (29.0)	
≥ 70	43 (43.0)	130 (43.3)	
Mean (SD) age in years	66.9 (11.1)	66.9 (10.9)	
Min-Max age in years	42-90	43-89	
Gender			1.000
Male	32 (32.0)	96 (32.0)	
Female	68 (68.0)	204 (68.0)	
Duration of DM in years			0.584
<5	20 (20.0)	75 (25.0)	
5-10	68 (68.0)	191 (63.7)	
>10	12 (12.0)	34 (11.3)	

[a]Chi-square test; SD, standard deviation; DM, diabetes mellitus; Min, minimum; Max, maximum.

Table 2
Univariable conditional logistic regression analysis of characteristics associated with IS patients.

Characteristics	Cases *n* (%)	Controls *n* (%)	OR_c[a]	95%CI	*p*-value[a]
History of DLP					
No	79 (79.0)	296 (98.7)	1		
Yes	21 (21.0)	4 (1.3)	29.6	6.9-126.4	<0.001*
History of AF					
No	94 (94.0)	299 (99.7)	1		
Yes	6 (6.0)	1 (0.3)	17.9	2.2-149.5	0.001*
Diastolic BP in mmHg					
<90	87 (87.0)	293 (97.7)	1		
≥90	13 (13.0)	7 (2.3)	7.1	2.5-20.1	<0.001*
Systolic BP in mmHg					
<140	62 (62.0)	231 (77.0)	1		
≥140	38 (38.0)	69 (23.0)	2.2	1.3-3.8	0.003*

Table 2 (Continued)

Characteristics	Cases *n* (%)	Controls *n* (%)	OR_c [a]	95%CI	*p*-value[a]
HbA1c in %					
<7	15 (15.0)	139 (46.3)	1		
7-7.9	15 (15.0)	65 (21.7)	2.2	1.0-4.9	0.07*
8-8.9	85 (26.0)	48 (16.0)	5.6	2.6-12.0	<0.001*
≥9	44 (44.0)	48 (16.0)	9.5	4.6-19.8	<0.001*
History of CVD					
No	93 (93.0)	294 (98.0)	1		
Yes	7 (7.0)	137 (2.0)	3.5	1.2-10.4	0.024*
FPG in mg/dl					
<126	22 (22.0)	127 (42.3)	1		
≥126	78 (78.0)	173 (57.7)	3.4	1.9-6.3	<0.001*
Total Cholesterol in mg/dl					
<200	70 (70.0)	233 (77.7)	1		
≥200	30 (30.0)	67 (22.3)	1.5	0.9-2.6	0.113
Serum creatinine in mg/dl					
≤1	48 (48.0)	177 (59.0)	1		
>1	52 (52.0)	123 (41.0)	1.7	1.0-2.8	0.037*
Smoker					
No	86 (86.0)	273 (91.0)	1		
Yes	14 (14.0)	27 (9.0)	1.9	0.9-4.5	0.108
Alcohol drinks					
No	96 (96.0)	297 (99.0)	1		
Yes	4 (4.0)	3 (1.0)	4.0	0.9-17.9	0.070
Microvascular complications					
No	64 (64.0)	212 (70.7)	1		
1	22 (22.0)	68 (22.7)	1.1	0.6-1.9	0.741
>1	14 (14.0)	20 (6.6)	2.4	1.1-5.2	0.024*
Body mass index in kg/m^2					
18.5 - 22.9	34 (34.0)	88 (29.3)	1		
23.0 - 24.9	23 (23.0)	55 (18.3)	1.0	0.6-1.9	0.903
25.0 - 29.9	29 (34.2)	107 (35.7)	0.7	0.4-1.2	0.198
≥30.0	12 (10.1)	44 (14.7)	0.7	0.3-1.5	0.316
<18.5	2 (2.0)	6 (2.0)	0.9	0.2-4.6	0.892

[a] Univariable conditional logistic regression analysis performed on 100 matched pairs; IS, ischemic stroke; DLP, dyslipidemia; AF, atrial fibrillation; BP, blood pressure; HbA1c, hemoglobin A1c; CVD, cardiovascular diseases; FPG, fasting plasma glucose; OR_c, crude odds ratio; CI, confidence interval. *Significant at $p < 0.05$.

Table 3
Multivariable conditional logistic regression analysis of association between HBA1c levels and IS among study subjects.

Variables	OR_c	95%CI	*p*-value	OR_{adj}	95%CI	*p*-value
HBA1c in %						
<7	1			1		
7.0-7.9	2.2	1.0-4.9	0.07	2.2	0.8-5.8	0.117
8.0-8.9	5.6	2.6-12.0	<0.001*	7.9	3.0-20.9	<0.001*
≥9	9.5	4.6-19.8	<0.001*	10.9	4.3-27.9	<0.001*

OR_c, crude odds ratio; AIS, acute ischemic stroke; CI, confidence interval; OR_{adj}, adjusted odds ratio for history of DLP, history of AF, diastolic BP, systolic BP, history of CVD, FPG, serum creatinine, and microvascular complications. *Significant at $p < 0.05$.

levels result in greater levels of advanced glycation end products (AGEs) due to glycation, altering protein function of low density lipoprotein (LDL) at apo B; the abnormal LDL is then captured by macrophages leading to accumulation of fatty plague in the endothelial wall, causing endothelial malfunction, loss of elasticity and atherosclerosis (Martin *et al*, 2006), decreased cerebral blood flow and finally IS.

Disadvantage in our study were that it was hospital based at a single institution so it cannot be applied to other populations.

In summary, in our study we found a significant association between higher HBA1c levels and ischemic stroke. Further prospective studies are needed in this study population to determine if an intervention to lower the HBA1c level will reduce the risk for stroke.

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REFERENCES

Air EL, Kissela BM, Diabetes, the metabolic syndrome, and ischemic stroke; epidemiology and possible mechanisms. *Diabetes Care* 2007;30:3131-40.

Banerjee C, Moon YP, Paik MC, *et al*. Duration of diabetes and risk of ischemic stroke: the Northern Manhattan Study. *Stroke* 2012;43:1212-7.

Bennett DA. Methodology of the global and regional burden of stroke study. *Neuroepidemiology* 2012;38:30-40.

Bureau of Policy and Strategies, Ministry of Public Health. Public health statistics 2010. Bangkok: The War Veterans Organization of Thailand, 2010.

Bureau of Policy and Strategies, Ministry of Public Health. Public health statistics 2015. Bangkok: The War Veterans Organization of Thailand, 2016a.

Bureau of Policy and Strategies, Ministry of Public Health. Thailand health profile 2011-2015. Bangkok: The War Veterans

Organization of Thailand, 2016b.

Dhamasaroja P. Baseline characterisitics of patients with acute ischemic stroke in suburban area of Thailand. *J Stroke Cerebrovasc Dis* 2008;17:82-5.

Dupont WD. Power calculations for matched case-control studies. *Biometrics* 1988; 44: 1157-68.

Feigin VL, Forouzanfar MH, Krishnamurthi R, *et al*. Global and regional burden of stroke during 1990-2010: findings from the Global Burden of Disease Study 2010. *Lancet* 2014;383(9913):245-54.

Feigin VL, Krishnamurthi R. Epidemiology and risk factors: global burden of stroke. In: Grotta JC, Albers GW, Broderick JP, *et al*, eds. Stroke: pathophysiology, diagnosis and management. 6th ed. China: Elsevier, 2016:165-206.

Gerstein HC, Miller ME, Byington RP, *et al*. Action to control cardiovascular risk in diabetes study group. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008;358:2545-59.

Hanchaiphiboolkul S, Puthkhao P, Towanabut S, *et al*. Factors predicting high estimated 10-year stroke risk: Thai Epidemiology Stroke Study. *J Stroke Cerebrovasc Dis* 2014;23;1969-74.

Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008;359:1577-89.

Johnston SC, Mendis S, Mathers CD. Global variation in stroke burden and mortality: estimates from monitoring, surveillance, and modelling. *Lancet Neurol* 2009;8:345-54.

Mackay J, Mensah GA. The atlas of heart disease and stroke. Geneva: World Health Organization, 2004.

Martin A, Rojas S, Chamorro A, Falcón C, Bargalló N, Planas AM. Why does acute hyperglycemia worsen the outcome of transient focal cerebral ischemia? Role of corticosteroids, inflammation, and protein O-glycosylation. *Stroke* 2006;37:1288-95.

Murray CJ, Ezzati M, Flaxman AD, *et al*. GBD 2010: design, definitions, and metrics. *Lancet* 2012;380(9859):2063-6.

Najarian RM, Sulivan LM, Kannel WB, Wilson PW, D'Aqostino RB, Wolf PA. Metabolic syndrome compared with type 2 diabetes mellitus as a risk factor for stroke: the Framingham Offspring Study. *Arch Intern Med* 2006;166:106-11.

Nilanont Y, Nidhinandana S, Suwanwela NC, *et al*. Quality of acute ischemic stroke care in Thailand: a prospective multicenter countrywide cohort study. *J Stroke Cerebrovasc Dis* 2014;23:213-9.

Patel A, MacMahon S, Chalmers J, *et al*. Advance Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008;358:2560-72.

Sacco RL, Shi T, Zamanillo MC, Kargman DE. Predictors of mortality and recurrence after hospitalized cerebral infarction in an urban community: the Northern Manhattan Stroke Study. *Neurology* 1994;44: 626-34.

Strong K, Mathers CD, Bonita R. Preventing stroke: saving lives around the world. *Lancet Neurol* 2007;6:182-7.

Suwanwela NC. Stroke epidemiology in Thailand. *J Stroke* 2014;16:1-7.

UK Prospective Diabetes Study Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;352:837-53.

World Health Organization (WHO). Use of glycated haemoglobin (HbA1c) in the diagnosis of diabetes mellitus: abbreviated report of a WHO Consultation. Geneva: WHO, 2001. *WHO/NMH/CHP/CPM/11.1*.