Relationship between hypercholesterolemia and acute ischemic stroke among patients with type-2 diabetes: A case control study

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Abstract

Objectives: To identify the association of high blood cholesterol with the risk of acute ischemic stroke (AIS) among Thai patients with type-2 diabetes (PTDs).

Methods: A case control study was conducted among PTDs attending Bhuddasothorn Hospital in Chachoengsao, with 100 cases and 300 controls from 2013-2016. Cases and controls were matched by sex, age (±5 years), residential area and attendance duration. Data were collected using questionnaires comprising two parts: demographic characteristics and medical data. Conditional logistic regression was applied to estimate the effect of high blood cholesterol on acute ischemic stroke among PTDs.

Results: Univariable conditional logistic regression showed risk factors for AIS among TPDs comprised history of atrial fibrillation, diastolic blood pressure, systolic blood pressure, HbA1c, history of CVD, FPG, total cholesterol, LDL cholesterol, creatinine, and microvascular complications (p<0.05). For multivariable conditional logistic regression analysis, controlling for possible confounding factors revealed a total cholesterol level of 240-279 mg/dl and higher increased the risk of AIS by a factor of 4.3 and 7.7 times, respectively (OR=4.3, 95%CI =1.4-13.7; OR=7.7, 95%CI =1.1-57.5).

Conclusion: A surveillance system of blood cholesterol among risk groups should be conducted in cooperation with information regarding cholesterol control and stroke prevention as an essential measure to reduce AIS risk.

Introduction

Cerebrovascular diseases (CVD) mainly include ischemic stroke and hemorrhagic stroke. At present, it has been well established that stroke is the second leading cause of death [1,2]. Its social burden increased from 38 to 61 million stroke cases between 1990 and 2020 [3]. The Global Burden of Diseases, Injuries, and Risk factors Study (GBD) reported approximately 16.9 million new stroke cases in 2010 [4]. Most comprised ischemic stroke (11.6 million cases) ending in 2.8 million deaths [4-7]. The GBD has predicted 12 million deaths and 200 million disability-adjusted life years (DALYS) lost to stroke in 2030 [4]. In Thailand, stroke is a major health burden and the leading cause of death and long term disability among the elderly [8]. According to epidemiology data from the Thai's Ministry of Public Health, over 50,000 stroke deaths occur annually, presenting an increasing trend of stroke death rate during the past 10 years, as shown in (Figure 1) [9,10].

Similar to other parts of the world, ischemic stroke is the most common stroke type in the Thai population. Causes of ischemic stroke are likely to be multifactorial. Effects of hypercholesterolemia showed a higher risk of ischemic stroke, mainly in western countries [11-15]. In Thailand, quite a few studies have reported this association among patients with type-2 diabetes. Therefore, the purpose of the study was to determine the association between high blood cholesterol and AIS occurrence among PTDs.

Variable definitions

Ischemic stroke is caused by a critical reduction of regional cerebral blood flow when the critical blood flow reduction lasts beyond a critical duration. One of the most widely used stroke schemes is the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification, which divides ischemic stroke in five categories: large artery atherosclerosis, cardiac embolism, small artery/lacunar occlusion, stroke of other determined etiology and stroke of undetermined etiology [16-19]. Ischemic stroke diagnosis is determined based on the code of I63, the International Classification of Diseases, 10th revision (ICD-10).

Hypercholesterolemia is a condition of high blood cholesterol. The National Heart, Lung and Blood Institute within the National Institutes of Health classifies total cholesterol of less than 200 mg/dl as desirable, 200-239 mg/dl as borderline high, and ≥240 mg/dl as high [20].
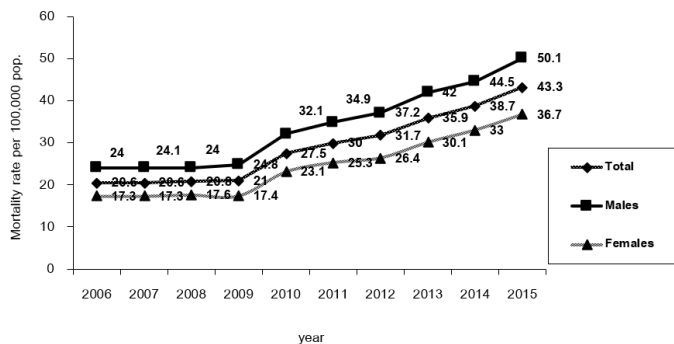
Figure 1. Mortality Rate of Stroke, Thailand, 2006-2015

Source: Bureau of Policy and Strategy, Ministry of Public Health [9,10]

Methods

Study design, sample size and sampling technique

A hospital-based matched case control study (1:3) was conducted at the Bhuddasothorn Hospital, Chachoengsao from 2013 to 2016 to identify the effect of blood cholesterol and AIS risk among PTDs. A total of 100 AIS cases and 300 controls were included in the study. The cases comprised PTDs newly diagnosed with AIS by neurologists and computer tomography scan. The controls comprised PTDs without AIS. Of the 400 participants, cases and controls were matched by age (±5 years), residential area and duration of attending. Both cases and controls used medical records comprising demographic factors, medical data and AIS status. The sample size was calculated using Stata 12 [21], where Po (0.04) and P1 (0.138) constituted the proportions of exposure in controls and cases, respectively [22]; $Z\alpha/2=1.96$ at $\alpha=0.05$; $Z\beta=0.84$ at $\beta=0.20$. The calculated sample size was at least 91 among cases and 273 among controls. Subjects totalled 100 cases and 300 controls for the present study. The authors used the average medical data during the past three years for exposed factors.

Ethics approval

The study protocol was reviewed and approved by the Ethics Committee for Research in Human Subjects of the Faculty of Public Health, Mahidol University (171/2557), the Ethics Committee for Research in Human Subjects of the Chachoengsao Public Health Office (PH_CCO_REC 004/58) and the Ethics Committee for Research of Buddasothorn Hospital (BSH-IRB 005/2558). The information was collected using medical records. Confidentiality was maintained using an anonymous technique throughout the study to ensure privacy and the results were analysed as a whole group.

Statistical analyses

The data were analyzed using STATA (Release 12, StataCorp LP, College Station, TX, Serial number: 4012044037). Data were tabulated by means of descriptive statistics, univariable analyses and multivariable analyses. Categorical variables were given as frequency and percentage, crude odds ratio, 95% confidence interval (CI) of OR and p-value. The numerical variables were expressed as mean, minimum and maximum and standard deviation (SD). Univariable conditional logistic regression analysis was performed to differentiate proportional exposures between PTDs with AIS and controls for categorical variables. Adjusted odds ratio and the 95% CI of OR were calculated from multivariable conditional logistic regression to examine associations between high blood cholesterol and AIS occurrence, adjusted for potential

confounding factors. A p-value of <0.05 was considered statistically significant in the analyses.

Results

Demographic characteristics

A total of 400 PTDs participated in the case control study. The average age of subjects was 67 years and (Table 1) outlines their demographic characteristics. To summarize, the majority were aged ≥70 years (43.0%, 43.3%), female (68%), and duration of DM was 5 to 10 years (68.0%, 63.7%). As shown in Table 1, no significant difference was observed regarding demographics at baseline among PTDs (p >0.05) (Table 1).

AIS and risk factors

Using univariable conditional logistic regression, we found possible risk factors of AIS among PTDs included history of AF, diastolic BP, systolic BP, HbA1c, history of CVD, FPG, total cholesterol (TC), LDL cholesterol, creatinine and microvascular complications (p <0.05), as shown in (Table 2). Concerning multivariable conditional logistic regression analysis, TC showed association with AIS occurrence after controlling for possible confounding factors (history of AF, diastolic BP, systolic BP, HbA1c, history of CVD, FPG, creatinine and microvascular complications), (Table 3) and higher TC was significantly associated with increased risk of AIS. Risk of developing AIS with TC 240-279 mg/dl2 and higher were 4.3 and 7.7 times, respectively, when compared with those of TC <200 mg/dl2 (ORadj= 4.3, 95%CI=1.4-13.7; ORadj= 7.7, 95%CI=1.1-57.5), as shown in (Table 3).

Discussion

Study participants comprised PTDs attending Bhuddasothorn Hospital, Chachoengsao Province. Most comprised females (68%) aged ≥70 years (43%). Results of multivariable analyses showed an association between TC and AIS among PTDs when controlling potential factors, which was consistent with related studies [23-25], while some studies found no association [26,27]. The present study showed 23% of TC ≥240 mg/dl among PTDs with AIS.

Hypercholesterolemia was able to cause stroke because continual high blood cholesterol would accumulate fatty plaque at the endothelial wall causing the endothelial wall to malfunction, and lose elasticity

Table 1. General characteristics of study subjects

Characteristics	Cases (n=100)		Controls (n=300)		p-value[a]
	n	%	n	%	
Age gr. (yrs)					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)	66.9 (11.1)		66.9 (10.9)		
Min-Max	42-90		43-89		
Sex					1.000
Male	32	32.0	96	32.0	
Female	68	68.0	204	68.0	
Duration of DM (yrs)					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

Table 2. Univariable conditional logistic regression analysis of factors associated with AIS among PTDs

Characteristics	Cases		Controls		OR$_c$	95%CI	p-value[a]
	n	%	n	%			
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 (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 (mmHg)							
<140	62	62.0	231	77.0	1		
≥140	38	38.0	69	23.0	2.2	1.3-3.8	0.003*
HbA1c (%)							
<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 (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 (mg/dl)							
<200	70	70.0	233	77.7	1		
200-239	7	7.0	53	17.7	0.4	0.2-1.0	0.060
240-279	18	18.0	12	4.0	5.9	2.7-12.9	<0.001*
≥280	5	5.0	2	0.6	8.2	1.5-43.7	0.013*
LDL Cholesterol (mg/dl)							
<100	42	42.0	126	42.0	1		
100-129	23	32.0	105	35.0	0.7	0.4-1.2	0.213
130-159	12	12.0	49	16.4	0.8	0.4-1.7	0.531
160-189	17	17.0	16	5.3	3.1	1.4-6.8	<0.006*
≥190	6	6.0	4	1.3	5.7	1.3-24.6	0.020*
HDL Cholesterol (mg/dl)							
>60	5	5.0	29	9.7	1		
41-59	36	36.0	97	32.3	2.1	0.8-5.6	0.159
≤40	59	59.0	174	58.0	1.9	0.7-5.2	0.216
Triglyceride (mg/dl)							
<150	52	52.0	187	62.3	1		
150-199	26	26.0	58	19.3	1.6	0.9-2.9	0.084
≥200	22	22.0	55	18.3	1.5	0.8-2.7	0.196
Creatinine (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*
Active smoking							
No	86	86.0	273	91.0	1		
Yes	14	14.0	27	9.0	1.9	0.9-4.5	0.108
Alcohol consumption							
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 (kg/m²)							
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, AIS=Acute ischemic stroke, 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-value < 0.05

Table 3. Multivariable conditional logistic regression analysis of cholesterol associated with AIS patients

Variables	OR_c	95%CI	p-value	OR_{adj}	95%CI	p-value
Total Cholesterol (mg/dl)						
<200	1			1		
200-239	0.4	0.2-1.0	0.058	0.8	0.4-1.7	0.069
240-279	5.4	2.3-12.9	<0.001	4.3	1.4-13.7	0.013*
≥280	8.2	4.6-19.8	0.013	7.7	1.1-57.5	0.045*
LDL Cholesterol (mg/dl)						
<100	1			1		
100-129	0.7	0.4-1.2	0.213	0.7	0.4-1.5	0.409
130-159	0.8	2.3-12.9	0.531	0.5	0.2-1.3	0.153
160-189	3.1	2.3-12.9	0.006	2.6	0.9-6.7	0.055
≥190	5.7	4.6-19.8	0.020	5.0	0.7-33.8	0.097

OR_c = crude odds ratio, AIS=acute ischemic stroke, CI=confidence interval
OR_{adj} = adjusted odds ratio for history of AF, diastolic BP, systolic BP, HbA1c, history of CVD, FPG, creatinine, and microvascular complications
*Significant at p-value < 0.05

leading to atherosclerosis [28, 29]. Accumulated plaque would cause endothelial stenosis and occlusion, and reduce cerebral blood flow (CBF). When CBF is insufficient for the brain tissue, the brain cells would die and cause the ischemic stroke.

Additionally, ischemic stroke might be a result of acute cerebral stenosis. After atherosclerosis, endothelial inflammation would inevitably appear, and causing a fracture in the fatty plaque, activating the accumulation of blood platelets followed by acute stenosis [28,29] and acute ischemic stroke [30,31].

Primary prevention involves appropriate dietary control, for example, using the dietary approach to stop hypertension [32,33], e.g., maintaining a cereal, vegetables, fruit and low fat diet. PTDs constitute a risk group for stroke [14,34]. Therefore, glycemic control at normal level should be practiced continually to help reduce AIS risk. Currently, the American Heart Association and the American Stroke Association recommend that the ideal glucose level after AIS is between 140 to 180 mg/dl [34]. In addition, PTDs mostly present hypertension [35]. Therefore, hypertension control constitutes a crucial factor in reducing stroke risk [36,37]. At present, many tools are available to evaluate stroke, namely, the Stroke Risk Calculator, Stroke Risk Quiz of the American Heart Association/American Stroke Association, the National Institute of Health Stroke Scale (NIHSS) Neurologic Examination, ABCD2 score and others. For Thais aged 35 to 70 years, the Thai CV risk score was made to evaluate stroke.

In summary, a surveillance system of blood cholesterol among risk groups should be conducted along with providing knowledge of stroke and self-care prevention, implementing health promoting campaigns including proper regular exercise, healthy diet, weight control, risk avoidance such as smoking and alcohol consumption, and basic techniques for maintaining a healthy lifestyle among risk groups, as they will help extensively reduce risk of developing stroke [38-40].

Advantages and limitations of the study

This case control study had some advantages. First, Buddasothorn Hospital is the tertiary care centre for the east part of Thailand. Second, the subjects were easily identified and provided sufficient numbers.

Finally, cases were reduced classification bias. Some limitations of this study should be noted. First, the study was a hospital based matched case-control study; therefore, the representative target population couldn't be mentioned. Second, selecting suitable controls was difficult. However, we matched cases and controls by age, residence and duration of attending.

Conflict of interest

The authors have no conflicts of interest associated with the material presented in this paper.

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