Yonsei Medical Journal
Vol. 30, No. 3, 1989

Risk Factors of Ischemic Brain Stroke in Korean Diabetic Patients
— A Retrospective Study —

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In order to investigate the risk factors of ischemic brain stroke (IBS) in diabetic patients, we analyzed 416 cases selected from 6239 diabetic patients admitted to Severance Hospital from Jan. 1983 to Dec 1987. Two hundred and eight cases had IBS. The other 208 cases without IBS were selected as a control group by a stratified random sampling method. The two groups were compared using various clinical characteristics of diabetes mellitus (DM) and known risk factors of IBS. In diabetics with IBS, the duration of DM was longer (9.2±7.1 years), hypertension was more frequently associated (68.2%) and the serum cholesterol level was higher (213.0±55.2 mg/dl) than in diabetics withtout IBS (7.6±7.1 years, 32.1% and 192.1±44.8 mg/dl, respectively). By means of Stepwise Logistic Regression Analysis (SLRA), it was found that the strong risk factors were hypertension and serum cholesterol level. The serum triglyceride level, type of DM and response to diabetes treatment were also thought to be risk factors of IBS by the retrial of SLRA of residuals after exclusion of hypertension and serum cholesterol level. IBS was not significantly related to the duration of DM, fasting blood glucose level, body weight, glycosylated hemoglobin value, and serum high-density lipoprotein-cholesterol level.

Key Words: Risk factors, ischemic brain stroke, diabetes mellitus

Diabetes mellitus (DM) is a well-known risk factor of ischemic brain stroke (IBS). Ten to nineteen percent of patients with IBS have DM and 3.5 to 6.2% of diabetic patients develop an IBS, which is much higher than the incidence of the general population (Abbott *et al.* 1987; Dennis and Warlow 1987; Kannel and McGee 1979; Min *et al.* 1988; Park *et al.* 1977: Yang *et al.* 1982).

The pathogenetic mechanism of DM contributing to the development of peripheral vascular complications is unclear, but some studies suggest its correlation with changes in blood coagulation or blood flow, changes in platelets, influence of prostaglandin on platelets or vessels, hyperglycemia, microvascular disease and insulin. Lipid disorders or hypertension, known as atherogenic, are frequently associated with DM (Colwell *et al.* 1981; Ganda 1980, 1985; Ruderman and Haudenschild 1984). Grunnet (1963) suggested that cerebral atherosclerosis was related to the serum level of cholesterol and acetonuria, but not to the duration of DM, hypertension or sex.

In Korea, there have been many studies investigating the complications of DM (Kim *et al.* 1979; Koo *et al.* 1984; Lee *et al.* 1981; Lee *et al.* 1983; Lee and Jung *et al.* 1984; Lee and Yang *et al.* 1984; Lee *et al.* 1985; Moon *et al.* 1972), but none about the risk factors of IBS in diabetic patients. This study was conducted to investigate the risk factors of IBS in the diabetic patient.

MATERIALS AND METHODS

Patients

We selected 208 patients with IBS from 6239 diabetic patients who were admitted to Severance Hospital from Jan. 1983 to Dec. 1987. The mean age of patients with IBS was 62.6 years, and there were 114

Table 1. Distribution of age and sex of diabetic patients with IBS

Age (year)		Number	
Mean±SD	Range	Male	Female
62.6±9.2	26-84	114	94

Received February 27, 1989
Accepted May 8, 1989
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males and 94 females (Table 1).

Those patients with reactive hyperglycemia, use of steroid or hyperglycemic agents and secondary DM due to pancreatitis, Cushing's syndrome, liver cirrhosis, etc. were excluded. The patients were classified into insulin-dependent type (type I DM), non-insulin-dependent non-obese type (type IIa DM) and non-insulin-dependent obese type (Type IIb DM) according to the classification of the National Diabetes Data Group (1979). Diagnostic criteria of IBS were similar to that of the Harvard Cooperative Stroke Registry: large artery thrombosis, lacunae and embolism were identified by clinical and laboratory features (Mohr *et al.* 1978). Patients who did not undergo computerized tomographic brain scanning and patients with embolic IBS caused presumably by cardiac disease, demonstrated by consistent physical findings, compatible electrocardiographic or echocardiographic features, were also excluded.

Methods

Retrospective and cross-sectional methods were used by reviewing medical records of selected patients. Two hundred and eight diabetics with IBS were divided into five groups by year. A control group (208 cases) was selected from 6031 diabetics without IBS by a stratified random sampling method and they were not significantly different in age, sex and year from the diabetics with IBS. Year-matched sampling of the controls was adopted because the pattern of dietary habits and life style of hospitalized patients are closely related to the overall changes of Korean society year by year (Tchai 1985, 1988). Age-matched sampling was considered necessary because age is a well-known factor for IBS and DM (Kannel and Wolf 1983; Minaker 1987). Those with previous IBS were excluded from the control group.

The clinical characteristics of DM evaluated were type of DM, percentage of present body weight (PBW) to ideal body weight (IBW), duration of DM, response to previous diabetic treatment, fasting blood glucose level and value of glycosylated hemoglobin (HbA1c), previous IBS, hypertension, coronary heart disease, cardiac arrhythmia and level serum cholesterol, serum triglyceride and serum high-density lipoprotein-cholesterol (HDL-Chol). Response to previous diabetic treatment was classified as fair, poor or none (Fair: no diabetic symptom at the admission and HbA1c value below 6%, Poor: no symptom and HbA1c value over 6%, None; no previous diabetic treatment).

For statistical analysis, we performed an independent t-test to compare continuous variables and a Chi-square test to compare categorical variables by means of SPSS/PC+ (Norusis 1986). To determine the significant risk factors for IBS in diabetic patients, variables were further analyzed by Stepwise Logistic Regression Analysis (SLRA) of BMDPLR in BMDP (Engelman 1985), courtesy of the Yonsei University Computer Science Center.

RESULTS

Clinical characteristics of diabetic patients with and without IBS

The duration of DM was longer in diabetics with

Table 2-A. Clinical characteristics of diabetic patients with and without IBS

(Independent t-test)

	Diabetics with IBS	Diabetics without IBS	p-value
Duration of DM (year)	9.2±7.1 (n=184)	7.6±7.1 (n=201)	0.030
Percent of PBW to IBW (%)	108.9±15.9 (164)	108.0±17.1 (189)	0.579
Fasting Blood Glucose (mg/dl)	236.5±90.8 (207)	216.9±83.8 (200)	0.240
Glycosylated Hemoglobin (%)	7.6±1.8 (155)	8.3±2.5 (194)	0.004

IBS: ischemic brain stroke; DM: diabetes mellitus; PBW: present body weight; IBW: ideal body weight; (n=): number of observed cases

Table 2-B. Clinical characteristics of diabetic patients with and without IBS

(Chi-square test)

		Diabetics with IBS	Diabetics without IBS	p-value
Type of DM	I	12	4	0.062
	IIa	109	135	
	IIb	44	51	
		(n=165)	(n=190)	
Response to Previous Diabetic Treatment	Fair	40	23	0.131
	Poor	81	80	
	None	78	54	
		(n=199)	(n=157)	

IBS: ischemic brain stroke; DM: diabetes mellitus; (n=): number of observed cases

IBS than those without IBS (p=0.030). There was no significant difference in fasting blood glucose level and response to previous diabetic treatment between the two groups (p=0.240, 0.131, repectively), but the level of HbA1c was lower in the IBS group (p=0.004). The percentage of PBW to IBW between the two groups was not significantly different (p=0.579). Type I DM, though not clear, seemed to be prone to IBS (p=0.062) (Table 2-A, 2-B).

Known risk factors of IBS in diabetic patients with and without IBS

Serum cholesterol and triglyceride levels were higher in diabetics with IBS than diabetics without IBS (p=0.000, 0.088, respectively). However, there was no significant difference in the serum level of HDL-Chol between the two groups (p=0.373). Sixty-one cases (29.3%) of the IBS group had previous IBS. Hypertension was associated more frequently in the IBS

Table 3-A. Known risk factors of IBS in diabetic patients with and without IBS

(Chi-square test, n=208)

		Diabetics with IBS	Diabetics without IBS	p-value
Hypertension	Present	142	67	0.000
	Absent	66	141	
Coronary Heart Disease	Present	15	14	1.000
	Absent	193	194	
Cardiac Arrhythmia	Present	12	8	0.491
	Absent	196	200	

IBS: ischemic brain storke

Table 3-B. Known risk factors of IBS in diabetic patients with and without IBS

(Independent t-test)

	Diabetics with IBS	Diabetics without IBS	p-value
Serum Cholesterol level (mg/dl)	213.1±55.2 (n=207)	192.1±44.8 (n=199)	0.000
Serum HDL-Chol level (mg/dl)	39.3±14.2 (n=193)	37.9±14.0 (n=164)	0.373
Serum TG level (mg/dl)	181.5±89.2 (n=190)	164.5±97.6 (n=167)	0.088

IBS: ischemic brain stroke; HDL-Chol: high density lipoprotein-cholesterol; TG: triglyceride; (n=): number of observed case

Table 4. Summary of stepwise logistic regression analysis of clinical characteristics of DM and known risk factors of IBS

Step Number	Variable Entered	D.F.	Variable Removed	Log Likelihood	Improvement Chi-square	Improvement p-value	Goodness of Fit Chi-square	Goodness of Fit p-value
0				−225.573			451.146	0.000
1	Previous IBS	1		−186.716	77.714	0.000	373.432	0.028
2		1	Previous IBS	−225.573	77.714	0.000	451.146	0.000
3	Hypertension	1		−206.111	38.924	0.000	412.222	0.001
4	Cholesterol	1		−201.920	8.382	0.004	403.840	0.001

IBS: ischemic brain stroke; DM: Diabetes Mellitus; D.F.: degree of freedom

Table 5. Summary of stepwise logistic regression analysis for residuals excluding hypertension and cholesterol

Step Number	Variable Entered	D.F.	Variable Removed	Log Likelihood	Improvement Chi-square	Improvement p-value	Goodness of Fit Chi-square	Goodness of Fit p-value
0				−146.909			293.819	0.000
1	Triglyceride	1		−144.084	5.651	0.017	288.168	0.000
2	Treatment	2		−140.656	6.855	0.032	281.313	0.000
3	DM type	2		−137.915	5.482	0.064	275.830	0.001

Treatment: response to previous diabetic treatment; DM: diabetes mellitus;
D.F.: degree of freedom

group than control group (p=0.000). No significant difference in the occurrence of coronary heart disease and cardiac arrhythmia was noted between the two groups (p=1.000, 0.491, respectively) (Table 3-A, 3-B).

Determination of risk factors of IBS by stepwise logistic regression analysis

Variables included for the analysis were duration of DM, hypertension, serum level of cholesterol, previous IBS, coronary heart disease, cardiac arrhythmia, serum level of triglyceride and serum level of HDL-Chol. Hypertension and serum level of cholesterol were found to be strong risk factors of IBS (p-value in goodness of fit=0.001 for both) (Table 4). Serum level of triglyceride, response to previous diabetic treatment and type of DM were thought to be significant risk factors by the retrial of SLRA of residual variables after exclusion of hypertension and serum level of cholesterol (p-value in goodness of fit=0.000, 0.000, 0.001, respectively) (Table 5).

DISCUSSION

Risk factors of IBS previously reported include old age, male sex, hypertension, transient ischemic attack, hypertensive heart disease, coronary heart disease, congestive heart failure, cardiac arrhythmia, diabetes mellitus, previous IBS, obesity, hyperlipidemia and lipoprotein disorder (Davis *et al.* 1987; Dennis and Warlow 1987; Dyken *et al.* 1984; Kagan *et al.* 1980; Kannel and Wolf 1983; Wolf *et al.* 1986). Regarding DM as a risk factor, there have been few studies which investigated the clinical characteristics closely associated with IBS. Grunnet (1963), in the autopsy study of 107 diabetic patients, found that those with a high serum cholesterol level or acetonuria had a high incidence or severe degree of atherosclerosis of cerebral vessels, but the duration of DM, hypertension and sex were not related with the severity and incidence of atherosclerosis. In contrast, our study showed that hypertension, serum cholesterol level, serum triglyceride level, type of DM and response to previous diabetic treatment were significantly related with IBS in diabetic patients.

There are various opinions about the effect of serum lipid on atherosclerosis. The prevailing views are that an increase of serum total cholesterol and triglyceride and a decrease of HDL-Chol cause arteriosclerosis or atherosclerosis (Bihari-Varga *et al.* 1981; Bradby *et al.* 1978; Colwell *et al.* 1981; Ganda 1980, 1985; Goldberg 1981; Grunnet 1963; Kim *et al.* 1974; Laakso *et al.* 1988; Nubiola *et al.* 1981; Reaven 1987; Ruderman and Haudenschild 1984; Tell *et al.* 1988). Diabetic patients show a greater atherogenic lipid or lipoprotein profile than non-diabetic patients (Goldberg 1981; Laakso *et al.* 1988; Uusitupa *et al.* 1986), though serum lipids or their metabolism seemed to be altered after a stroke (Mendez *et al.* 1987). In our study, serum cholesterol level was determined as a strong risk factor of IBS and serum level of triglyceride was thought to be another risk factor after exclusion of the influence of cholesterol. HDL-Chol had no significance.

Hypertension was associated with IBS in about 40-65% of cases (Chung *et al.* 1978; Min *et al.* 1988; Yang *et al.* 1982). It was also associated with 28-58% of diabetic patients, which is higher than non-diabetics (Han *et al.* 1974; Kim *et al.* 1979; Laakso *et al.* 1988; Moon *et al.* 1972; Sprafka *et al.* 1988). In our study, hypertension was more frequently associated with IBS and was a strong risk factor of it. Sprafka *et al.* (1988) suggested that hypertension in diabetic patients is more closely related to old age, female sex and body mass index, not to the control of hyperglycemia, diabetic control and the duration of DM. Our study was designed to be age-and sex-matched in the sampling of the control group and showed no significant difference in body weight or fasting blood glucose level between the two groups, which excluded the influences of these variables on the occurrence of hypertension.

Only type I DM showed an increased incidence of IBS; however, the number of cases of type I was too small to classify it as an important risk factor of IBS. In addition, the percentage of PBW to IBW was not significantly related to IBS. However, type I DM was found as a significant risk factor by SLRA.

In fact, the HbA1c value reflects whether the blood glucose level has been well controlled in diabetic patients (Gabbay *et al.* 1977), but there are various opinions on the relationship of the HbA1c value and response to diabetic treatment with cardiovascular complications. Riddle and Hart (1982) found that the HbA1c value was higher in IBS patients and transient ischemic attack patients regardless of previous diabetic treatment. Kim *et al.* (1984) suggested that the HbA1c value in diabetics with vascular complications was lower than in those without. Hanssen *et al.* (1986) and Knatterud (1978) had opposite views to each other. The one showed that a microangiopathic complication was decreased by good control of the blood glucose level. The other found that there was no change in the incidence of vascular complications despite appropriate control of the blood glucose level by insulin. Similar to Kim *et al.* (1984) and Knatterud (1978),

our study revealed that the HbA1c value was lower in the IBS group and the response to previous diabetic treatment was related to IBS rather disproportionately in the univariate analysis. Fasting blood glucose level was not significantly related to IBS. In addition, the possibility of reactive hyperglycemia caused by IBS (Melamed 1976) per se made it invalid to analyze the variable statistically.

Coronary heart disease and cardiac arrhythmia are recognized as risk factors of IBS (Dennis and Warlow 1987; Dyken *et al.* 1984; Kagan *et al.* 1980; Kannel and Wolf 1983; Wolf *et al.* 1986). Our study was directed to evaluate risk factors of non-embolic IBS and those two risk factors were mostly excluded through the sampling procedure, which made it difficult to determine their significance as risk factors.

In summary, the risk factors of IBS in DM were considered to be hypertenison, high serum cholesterol level, high serum triglyceride level, type I DM and fair response to previous diabetic treatment, though the latter two were not easily acceptable. IBS was not significantly related to the duration of DM, fasting blood glucose level, body weight, HbA1c value and serum HDL-Chol level.

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