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Original Articles

The Relative Risk Assessment of Leptin for Stroke in Korea

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Leptin has a close correlation with obesity, which is known to be a major factor for stroke. This study was performed to determine whether serum leptin level would be an independent risk factor for stroke and whether it would change significantly early after stroke.

Subjects were selected from those within 1 month after onset and non-stroke referents at Kyung Hee Oriental Medical Center in Seoul, Korea. We compared leptin and the other characteristics between stroke subjects and referents. Body mass index, hypertension history, presence of drinking and smoking, waist/hip ratio, total cholesterol and triglyceride were recorded. To assess odds ratio of leptin for stroke, we used logistic regression analysis. Leptin was rechecked 2 weeks later and compared with the former value in acute stroke subjects.

In this study, serum leptin did not differ significantly between stroke subjects and referents, and its odds ratio was not significant in male (OR=0.52, 95% CI; 0.13-2.08) and female (OR=1.57, 95% CI; 0.53-4.67). In acute stroke subjects, leptin did not change significantly 2 weeks later. Hypertension had a significant odds ratio in male (OR=3.39, 95% CI; 1.02-11.24) and female (OR=12.37, 95% CI; 3.67-41.65). High waist/hip ratio was only in female (OR=6.70, 95% CI; 1.73-26.02).

In conclusion, leptin was not an independent risk factor for stroke and its serum level did not change significantly early after stroke. Hypertension and waist/hip ratio had significant relative risks. *(Korean J of Oriental Med 2003;24(4):1-5)*

Key Words: leptin, stroke

Introduction

Leptin is a protein hormone with important effects in regulating body weight, metabolism and reproductive function[1)]. The protein is encoded by the obese (ob) gene and is expressed predominantly by adipocytes, which fits with the idea that body weight is sensed as the total mass of fat in the body. Smaller amounts of leptin are also secreted by cells in the epithelium of the stomach and in the placenta. Leptin receptors are highly expressed in areas of the hypothalamus known to be important in regulating body weight, as well as in T lymphocytes and vascular endothelial cells[2,3)].

The mechanisms by which leptin exerts its effects on metabolism are largely unknown and are likely quite complex. However, considering that leptin is associated with obesity and insulin resistance syndrome, which are moderate risk factors for stroke, there seems to be a causal relationship between leptin and stroke. In this study, we examined the relative risk of leptin for stroke

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and the change of leptin early after stroke.

Methods and Materials

We selected stroke subjects (within 1 month after onset) hospitalized at the Department of Circulatory Internal Medicine, Kyung Hee Oriental Medical Center, Seoul, Korea, from November 1, 1997 to June 30, 1999. Diagnosis was confirmed by Brain CT or MRI. Referents were composed of healthy subjects without any cardiovascular events from out-patients of the same hospital.

At the time of admission, we checked serum leptin, body mass index (BMI), hypertension history, habits of drinking and smoking, waist/hip ratio (W/H ratio), total cholesterol (T-cholesterol) and triglyceride. These were compared between stroke subjects and referents. When stroke subjects were in the acute stage, i.e. within 1 week after onset, their leptin were rechecked 2 weeks later.

As to the statistical analysis, we compared characteristics of stroke subjects and referents with independent *t*-test and chi-square test. *P*-value under 0.05 was regarded as significance. To assess odds ratios, univariate and multivariate models of logistic regression analysis were used. The change of leptin was assessed by paired *t*-test.

Results

We analyzed our data according to the distinction of sex, because the normal ranges of leptin, W/H ratio and BMI differ by sex[4,5].

In males, leptin and other characteristics showed no significant difference between strokes and referents. Only hypertension was more common in male stroke cases (Table 1).

Univariate and multivariate logistic regression revealed that known hypertension was the only independent risk factor for stroke (OR=3.39, 95% CI;

Table 1. Subjects' Characteristics in Males

	Referents (n=21)	Cases (n=41)	*P*-value
Age	59.7±9.6	60.5±9.7	NS
Body Mass Index	23.1±2.9	23.6±3.0	NS
T-cholesterol	190.1±27.4	184.9±41.1	NS
Triglyceride	149.0±65.9	192.5±213.3	NS
Hypertension	6 (28.6%)	23 (56.1%)	0.04
Regular smoking	12 (57.1%)	32 (78.0%)	NS
Alcoholic drinking	12 (57.1%)	28 (68.3%)	NS
Leptin	4.2±2.3	4.0±2.2	NS
W/H ratio	0.92±0.09	0.94±0.05	NS

*: Independent *t*-test for continuous variables and chi-square test for categorical variables

Table 2. Univariate and Multivariate Logistic Regression in Males

Variables	Range	Referents	Cases	cOR*	95% CI	aOR**	95% CI
Leptin(μg/L)	≤ 5.6	16	34	1.00		1.00	
	> 5.6	5	7	0.66	0.18-2.40	0.52	0.13-2.08
W/H ratio	< 0.89	20	35	1.00		1.00	
	≥ 0.89	1	6	1.58	0.42-5.53	1.09	0.27-4.41
Hypertension	Yes	6	23	3.19	1.30-9.89	3.39	1.02-11.24
	No	15	18	1.00		1.00	

* cOR: Crude odds ratio ** aOR: Adjusted odds ratio

Table 3. Subjects' Characteristics in Female

	Referents (n=32)	Cases (n=52)	*P*-value
Age	59.4±7.5	63.1±11.5	NS
Body Mass Index	24.7±2.9	24.3±3.2	NS
T-cholesterol	200.9±37.5	192.6±40.6	NS
Triglyceride	144.4±83.1	146.1±67.2	NS
Hypertension	6 (18.8%)	36 (69.2%)	< 0.001
Regular smoking	1 (3.1%)	2 (3.8%)	NS
Alcoholic drinking	3 (9.4%)	4 (7.7%)	NS
Leptin	9.9±6.3	11.7±5.9	NS
W/H ratio	0.90±0.05	0.93±0.05	0.023

*: Independent *t*-test for continuous variables and chi-square test for categorical variables

Table 4. Univariate and Multivariate Logistic Regression in Female

Variables	Range	Referents	Cases	cOR*	95% CI	aOR**	95% CI
Leptin(μg/L)	≤ 11.1	21	28	1.00		1.00	
	> 11.1	11	24	1.64	0.66-4.01	1.57	0.53-4.67
W/H ratio	< 0.88	13	7	1.00		1.00	
	≥ 0.88	19	45	4.40	1.52-12.75	6.70	1.73-26.02
Hypertension	Yes	6	36	9.75	3.36-28.29	12.37	3.67-41.65
	No	26	16	1.00		1.00	

* cOR: Crude odds ratio ** aOR: Adjusted odds ratio

Table 5. The Changes of Serum Leptin early after Stroke (n=93)

	Baseline	2 weeks later	*P*-value
Leptin	8.76 ± 5.39	8.34 ± 6.21	0.691

*: *P*-value was calculated from paired *t*-test

1.02-11.24, Table 2).

In females, stroke subjects were more often hypertensive and had higher W/H ratio than referents. The leptin did not differ between the two groups (Table 3).

Hypertension (OR=12.37, 95% CI; 3.67-41.65) and higher W/H ratio (OR=6.70, 95% CI; 1.73-26.02) were the predictors for stroke in logistic regression analysis (Table 4).

The serum leptin at 2 weeks later was lower than the initial value, but the difference was not significant (Table 5).

Discussion

This study examined leptin as a possible independent risk factor for stroke in a case-referent study. Leptin was discovered to be one of hormones encoded by the obese gene in 1994[6]. It is some kind of amino acid from adipose tissue. It is known to stimulate hypothalamus and inhibit the effects of starvation. It also elevates sympathetic nerve activity[7-9].

Recent researches have proved that leptin associates closely with the known risk factors for stroke. Elevated leptin level had a positive significant correlation with high blood pressure, thus it may contribute to hypertension[10,11]. Dysregulation of leptin reception by beta-cells may result in chronic hyperinsulinemia and may contribute to the pathogenesis of adipogenic diabetes[12,13]. Inversely, hyperglycemia for a long period and poorly controlled diabetes may reduce serum leptin[14,15].

Concerning cholesterol, leptin did not show the direct relationship with hypercholesterolemia.

Clinical trials on leptin and stroke itself have just begun. Leptin has been reported as a possible independent risk factor for stroke[16] and had a significant correlation with cerebral blood flow[17]. However, it is

not still definite that elevated leptin level could be a risk factor for stroke.

In our study, leptin was not an independent risk factor for stroke, and the average serum leptin levels of referents and strokes showed no significant difference.

These results are not in accord with Soderberg' s report[16], but considering that leptin couldn' t have a significant odds ratio in a univariate model even in Soderberg' s report, it does not seem to be strongly associated with stroke.

We used BMI and W/H ratio for evaluating obesity. BMI did not differ between stroke subjects and referents, which corresponds to previous reports saying that BMI is not an independent risk factor for stroke[18-20]. Nevertheless, there are not a few reports arguing the opposite[21-23].

Males showed no significant difference in W/H ratio between stroke subjects and referents, but W/H ratio of female stroke subjects was higher than referents. By logistic regression analysis, W/H ratio was an independent risk factor for stroke in females. The same results have been reported previously[18,24,25]. Hypertension, already proven to be a strong risk factor[26], was the only independent risk factor regardless of gender.

Concerning the change of serum leptin early after stroke, leptin was reported to have upward tendency for the first two days after stroke onset and showed an abnormal diurnal rhythmicity at the end of the first week[27]. We observed that leptin was lower 2 weeks later, but had no significance. This suggested that stroke occurrence seemed to have little effect on serum leptin level.

In conclusion, hypertension, BMI and W/H ratio showed similar results to previous reports, but leptin showed no direct correlation with stroke.

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