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Original Article

Coffee Consumption as a Risk Factor of Ischemic Cerebral Infarction in Koreans

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Background and Purpose : To prevent ischemic cerebral infarction, it is very important to reduce risk factors which might cause stroke. However, the relationship of coffee consumption with ischemic cerebral infarction still remains unclear. The purpose of this study was to investigate the effects of coffee consumption on the risk of ischemic cerebral infarction in Koreans.

Methods : A case-control study was conducted from April 1, 2001 to July 31, 2004. Cases (n=435) of first incident ischemic cerebral infarction were enrolled and were mostly matched by age to stroke-free hospital controls (n=407). All subjects were interviewed, examined and had anthropometric measurements by using an organized questionnaire. The coffee consumption was classified by the average frequency of intake, being none, 1 cup/day, 2-4 cups/day, more than 5 cups/day. Odds ratios (ORs) of ischemic cerebral infarction were proved multivariate analysis after adjustment for demographic factors, diet factors, and vascular risk factors.

Results : When adjusted for sex, age, and other factors, coffee consumption and stroke do not have a significant association. ($\leq$1 cup/day OR=1.035, 95 % CI=0.880-2.756; 2-4 cups/day OR=1.452, 95 % CI=0.864-2.440; $\geq$ 5 cups/day OR=1.557, 95 % CI=0.705-3.435)

Conclusions : In this study, we conclude that coffee consumption is not an important risk factor of ischemic cerebral infarction in Koreans. Prospective and cohort study on the relation between coffee consumption and the possibility of inducing ischemic cerebral infarctions in Koreans will be required in the future.

Key Words : coffee, ischemic cerebral infarction, Korean

Introduction

As the aging society sets in, health issues of the aged population are becoming a primary concern. Cerebrovascular disease was found to be the second leading cause of mortality and a leading cause of chronic disability and morbidity in Korea[1].

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Nowadays coffee has become one of the most favored beverages among the general public in the world.

There has been much research concerning the relationship between coffee consumption and a variety ofdiseases. However, there is still debate about the risk and benefit of this subject. Coffee consumption has been thought to have preventive effect upon type 2 DM[2,3], Parkinson's disease[4], and liver disease (hepatic injury, cirrhosis and hepatocellular carcinoma)[5,6]. However, in myocardial infarction such as cardiovascular disease, there have been reports that coffee consumption is a risk factor[7-9], while other studies say that it

does not have an effect on such diseases[10-12].

Prospective cohort studies have reported that there is no significant relationship between coffee consumption and stroke[13, 14]. However, there is a report that coffee consumption among hypertensive men in older middle-age has the possible risk of thromboembolic stroke[15], and high coffee consumption has the risk of aneurysmal SAH[16]. In domestic reports, research of Bu et al[17]. was the only Korean studythat has been undertaken on the Korean people. Even in her report, it only stated a possible connection between coffee and stroke.

The purpose of this study was to investigate the effects of coffee consumption on the risk of ischemic cerebral infarction in Koreans using case-control study of patients with first ischemic cerebral infarction and inpatient controls of the similar sex and age, thereby broadening Bu's investigation.

Material

1. Selection of Cases

Inpatients were recruited at Sangji Oriental Hospital from April 1, 2001 to July 31, 2004 with ischemic cerebral infarction according tothe guidelines of the Institutional Review Board of Sangji University Oriental Hospital. This study was approved by the Institutional Review Board of Sangji University Oriental Hospital. The researcher was provided with written informed consent from all participants.

Ischemic stroke was defined as an evidence of an infarction within one week of attack in a clinically relevant brain area by brain CT or MRI scan[18].

We excluded cases who had a transient ischemic attack (an event lasting < 24h), who died within 24 hours of admission, who had a history of stroke, who had deep-vein thrombosis, who had acute myocardial infarction, or who had major illness requiring surgery or bed rest of longer than a week.

2. Selection of Controls

Recruited controls were matched to cases by the difference of 5-year age at time of admission in Sangji University Oriental Hospital. Control subjects were eligible if they had never been diagnosed with stroke. The period was between April 1, 2001 to July 31, 2004.

We excluded cases who had a transient ischemic attack (an event lasting < 24h), who died within 24 hours of admission, who had a history of stroke, who had deep-vein thrombosis, who had acute myocardial infarction, or who had major illness requiring surgery or bed rest of longer than a week.

Methods

The study parameters were obtained from both case patients and control participants, and the data were collected through face-to-face interviews by trained research assistants, using a questionnaire adapted and revised by our research group.

The data were measured to assess age, sex, social economic status, lifestyle, coffee consumption, green tea consumption, dietary habits, educational level, maritalstatus, religion, family history of stroke, smoking status, alcohol consumption, systolic and diastolic blood pressure, and body mass index (BMI); fasting blood specimens for lipid, glucose, and cholesterol level were acquired.

The inquiries of coffee consumption were given on the average amount of coffee consu-

mption both during the past day and during the participant's drinking lifetime.

On the basis of past studies[7-9], we defined four categories of coffee consumption; never, ≤ 1 cup/day, 2-4 cups/day, and ≥ 5 cups/day.

BMI was calculated from body weight and height measured by a scale. Using the Detecto Floor Scales Model Ⅱ (Detecto, Inc., Brooklyn, New York), each participant's weight was measured to the nearest 0.5kg. Height was measured to the nearest 0.5cm using the standard vertical attached rod on the Detecto Floor Scales Model Ⅱ [19].

Total cholesterol and HDL cholesterol were measured according to standard practices[20]. Blood pressure was measured with the use of a calibrated standard aneroid sphygmomanometer. After the subject had 5 minutes of relative immobility in a sitting position, two blood pressure measurements separated by 15 minutes were recorded (as mean value of both times), 7 and 14 days after admission.

Blood samples were drawn within 72 hours of admission and sent for complete blood count on admission. Fasting glucose was measured with a Hitachi 747 automated spectrometer (Boehringer). Fasting lipid panels (including total cholesterol, LDL, HDL, and triglyceride) were measured with a Hitachi 705 automated spectrometer (Boehringer).

Standardized questions were developed and revised several times by our researcher group regarding the variables.

1. Statistical Analyses

Continuous variables were done with Student's t-test for comparing cases and controls means, and categorical variables were done using chi-square tests for comparisons between cases and controls values, which were about univariate testing of risk factors.

The relationship between coffee consumption and ischemic cerebral infarction was examined by estimating odds ratios from logistic regression. Stepwise logistic regression with forward inclusion of variables was used to model the probability of ischemic cerebral infarction as a function of the variables considered simultaneously. The binary response variable was defined as ischemic cerebral infarction and control. For the logistic regression analyses, four models were estimated. Model 1 was adjusted by sex and age, model 2 was additionally adjusted by diet factors such as green tea consumption and dietary habits, model 3 was supplementarily adjusted by vascular factors[1] such as smoking status, drinking status, family history of stroke, religion, and marital status, and model 4 was added with vascular factors[2] such as systolic and diastolic pressure, fast blood sugar (FBS), low density lipoprotein cholesterol, and anthrogenic index (LDL-C/HDL-C)[21].

Result

The basic characteristics of the 435 cases and the 407 controls are shown in Table 1. There were more female subjects than male subjects, but there was no significant difference in sex distribution between cases and controls. The age distribution was also similar in cases and control.

The cases disproportionately included persons who were current drinkers, had family history of stroke, and had higher mean of systolic blood pressure, diastolic blood pressure, LDL cholesterol, LDL-C/HDL-C, and FBS than that of controls. Green tea consumption and religion were more prevalent among controls. Cases and controls

Table 1. Distribution of Basic Characteristics of Cases and Controls

Variable		Controls(n=407)	Cases(n=435)	P value
sex(n, %)	Male (n=285)	126(31.0)	159(36.6)	0.94
	Female (n=557)	281(69.0)	276(63.4)	
Age(n, %)	≤49	71(17.4)	47(10.8)	0.09
	50-59	63(15.5)	77(17.7)	
	60-69	128(31.4)	146(33.6)	
	70-79	112(27.5)	131(30.1)	
	≥80	33(8.1)	34(7.8)	
coffee(no/day, %)	never	164(40.3)	167(38.4)	0.521
	≤1 cup	130(31.9)	132(30.3)	
	2-4 cups	87(21.4)	97(22.3)	
	≥5 cups	26(6.4)	39(9.0)	
green tea(n, %)	no	277(68.1)	330(75.9)	0.014
	yes	130(31.9)	105(24.1)	
smoking(n, %)	never	283(69.5)	270(62.1)	0.074
	past	46(11.3)	60(13.8)	
	current	78(19.2)	105(24.1)	
Alcohol drinking(n, %)	never	243(59.7)	217(49.9)	0.015
	past	43(10.6)	52(12.0)	
	current	121(29.7)	166(38.2)	
Dietary Habit(n, %)	meat preference	52(12.8)	79(18.2)	0.059
	vegetable preference	167(41.0)	154(35.4)	
	Both	188(46.2)	202(46.4)	
Family history of Stroke (n, %)	no	333(81.8)	303(69.7)	<0.001
	yes	74(18.2)	132(30.3)	
Marital Status	Current married	295(72.5)	292(67.1)	0.231
	Separation by death	104(25.6)	134(30.8)	
	Others	8(2.0)	9(2.1)	
Religion(n, %)	no	146(35.9)	189(43.4)	0.029
	yes	261(64.1)	246(56.6)	
Regular Exercise(n, %)	no	261(64.1)	324(74.5)	0.001
	yes	146(35.9)	111(25.5)	
Education level(n, %)	no	108(26.5)	153(35.2)	0.089
	primary school	154(37.8)	155(35.6)	
	middle school	54(13.3)	46(10.9)	
	high school	63(15.5)	56(12.9)	
	college and over	28(6.9)	25(5.7)	
BMI(kg/m2, n, %)	<25 (n=363)	193(47.4)	170(39.1)	0.588
	≥25 (n=290)	148(36.4)	142(32.6)	
SBP(mmHg, mean±SD)		133.43±16.01	147.52±19.10	<0.001
DBP(mmHg, mean±SD)		86.21±10.08	90.66±10.62	<0.001
TC(mg/dL, mean±SD)		188.71±37.35	196.00±38.67	0.17
LDLC(mg/dL, mean±SD)		114.18±73.58	121.99±35.86	0.009
HDLC(mg/dL, mean±SD)		44.75±11.55	43.57±13.67	0.259
LDL-C/HDL-C		2.69±0.88	2.96±1.05	<0.001
TG(mg/dL, mean±SD)		144.18±73.58	152.84±86.00	0.185
FBS(mg/dL, mean±SD)		101.09±32.46	114.98±44.28	<0.001

P-value of Chi-square test, student t-test All results were considered significant if $P<0.05$
BMI : Body Mass Index. Non obese <25kg/m^2, obese ≥25kg/m^2
LDL-C/HDL-C : Atherogenic index = Low density lipoprotein cholesterol/High density lipoprotein cholesterol
SBP=Systolic blood pressure, DBP=Diastolic blood pressure, TC=Total cholesterol, LDL-C=Low density lipoprotein cholesterol, HDL-C=High density lipoprotein cholesterol, TG=Triglyceride
FBS=Fasting Blood Serum

Table 2. Associations of Coffee consumption Status with Other Risk Factors

Models	Level of Coffee Consumption(OR(95 % CI))			
	None	≤1 cup/day	2-4 cups/day	≥5 cups/day
Crude	1.000	0.997(0.721-1.379)	1.095(0.763-1.571)	1.473(0.858-2.530)
Model 1	1.000	1.013(0.731-1.405)	1.133(0.779-1.647)	1.558(0.880-2.756)
Model 2	1.000	1.052(0.754-1.467)	1.134(0.777-1.655)	1.625(0.913-2.894)
Model 3	1.000	1.043(0.741-1.467)	1.140(0.769-1.689)	1.429(0.771-2.646)
Model 4	1.000	1.035(0.658-1.630)	1.452(0.864-2.440)	1.557(0.705-3.435)

Model 1 : The odds ratio adjusted for sex and age ; the 95 % confidence interval is for this odds ratio.
Model 2 : The odds ratio also adjusted for sex, age and diet factors, such as green tea consumption and dietary habits
Model 3 : The odds ratio also adjusted for sex, age, diet factors and vascular factors(1), such as, smoking status, drinking status, family history of stroke, religion status, martial status
Model 4 : The odds ratio also adjusted for sex, age, diet factors, vascular factors(1), and vascular factors(2), such as systolic and diastolic pressure, FBS, low density lipoprotein cholesterol, anthrogenic index(low density lipoprotein cholesterol/hight density lipoprotein cholesterol)
OR : Odd Ratio
95 %CI : 95 % confidence interval

had similar coffee consumption, smoking, dietary habits, marital status, and educational level, and had similar mean of total cholesterol, HDL-cholesterol, and triglyceride.

We also analyzed the associations between coffee consumption and the risk of ischemic cerebral infarction (Table 2).

Using the no coffee consumption group as a reference, the odds ratio (OR) values of ≤ 1 cup/day, 2-4 cups/day were almost equivalent to 1.00. However, for the ≥ 5 cups per day, the OR value of our crude model was 1.473 (95 % CI = 0.858-2.530), and the OR values of the stepwise adjusted models were 1.558 (95 % CI =0.880-2.756), 1.625 (95 % CI = 0.913-2.894), 1.429 (95 % CI = 0.771-2.646), and 1.557 (95 % CI = 0.705-3.435), with no statistical significance (Table 2).

Discussion and Conclusion

Coffee is a complex mixture of chemicals which include caffeine, cafestol, kahweol, chlorogenic acid, and micronutrients[22,23]. Caffeine, the primary substance of coffee, stimulates the central nervous system, elevates blood pressure acutely, increases metabolic rate, and causes diuresis[24]. Cafestol and kahweol have a cholesterol-raising effect[25]. Chlorogenic acid has been considered to have antioxidant activity *in vitro*[26].

Not many research reports exist on coffee consumption and ischemic cerebral infarction. In foreign research, A.A. Hakim et al.[15] reported that when adjusted for age, consuming coffee raised the risk of thromboembolic stroke significantly, and when adjusted for other factors, comparing those who drink three cups of coffee with those who do not drink any coffee, the former had at least two times the risk of ischemic cerebral infarction (RR=2.1; 95 % CI =1.2-3.7).

In domestic research, when Bu et al[17]. had adjusted for sex and age, only at 2-3 cups per day had shown the value of 1.782 (95 % CI = 1.032-3.079) for the OR showing statistical significance. When confounding variables such as sex, age, smoking, and drinking had been adjusted for, the value had no significance. However, since time and sample had limitations,

there was a need for expanding the samples.

Until now there has been no concrete study indicating the influence or mechanism of coffee consumption to ischemic cerebral infarction. However, synthesizing various studies, one could predict the possible influence of ischemic cerebral infarction by the following.

The primary substance which heightens the blood pressure after drinking coffee is known to be caffeine[27, 28].

Second, caffeine, which has been known as an adenosine receptor blockade, lowered regional cerebral blood flow which caused a higher possibility of stroke[29,30].

Third, increase in serum cholesterol could elevate the risk of thromboembolic stroke[31], and lipid-soluble fraction in unfiltered and boiled coffee could raise serum cholesterol levels[32, 33].

Fourth, the relationship between homocysteine and coffee consumption was related to the increase of ischemic cerebral infarction[34-37]. Several studies have indicated that coffee consumption causes an impairment of the flow-mediated dilatation in the brachial artery[38], stiffness in the aortic, and reflections of wave[39]. Also, endothelial dysfunction hindered the blood flow and caused an indirect effect on cerebro-vascular disease.

Finally, coffee consumption had an effect on coronary heart diseases[8].

Based on these theories, we have done a case-control study in Koreans and have come to think that coffee could be a risk factor of ischemic cerebral infarction. We analyzed the relationship between coffee consumption and ischemic cerebral infarction using logistic regression analyses.

While coffee consumption of ≥ 5cups per day had the value of 1.473～1.557 for the OR, the crude model and adjusted models had similar values, nonetheless without any significance (Table 2). After adjusting for all variables, neither Bu's study nor this study showed any significance. Coffee could not be as a crucial factor as stated above.

We did not examine the different types of coffee, and the research was done mostly among a rural population. We could speculate that the rural population consumes more instant coffee than filtered coffee. There are reports which state that filtered coffee, percolated coffee, and instant coffee all have smaller amounts of cafestol and kahweol (0.2-0.6 mg/cup)[40,41].

Cafestol and kahweol were diterpenes which continuously increased cholesterol ester transfer protein activity which then elevated LDL cholesterol[42]. Therefore, there could be other factors than sugar and cream which raise the level of LDL cholesterol.

By recent meta-analysis, a study of blood pressure, systolic blood pressure has increased significantly by 1.2 mmHg, while diastolic blood pressure increased by only 0.5 mmHg which was an insignificant amount. It was done through18 randomized controlled trials with a median duration of 43 days and a median intake of 725 ml/day[43]. While some reports state that there is no relationship between blood pressure and coffee[44,45], others report that it has an inverse association[46,47]. Considering these reports, we thought that coffee consumption could have a connection with blood pressure, but the association was insignificant, therefore consumption of coffee has a rare direct effect on stroke.

Even though there was a report that said coffee caused aortic stiffness and wave reflections[39], another report said that there was no significant

effect on endothelial dysfunction[48]; the subject remains controversial.

The primary risk factors of stroke are high blood pressure, diabetes mellitus, and hyperlipidemia. Since these three risk factors have a major influence as confounding variables, the OR of coffee in this study could be an insignificant amount.

There were more reports stating that there was no significant distinct relationship between coffee consumption and the risk factors of coronary heart disease[10-12].

Also, since recent cohort and related research report that cardiovascular disease and coffee consumption have no relationship[49-51], stroke and coffee could also have no significant effect.

Several important limitations of this study should be considered. First, in selection of the study, it was difficult to represent the total Korean population because it was selected from a number of inpatients from a fixed local hospital. Second, there is a possibility of recall bias in case-control studies, particularly in studies of imprecisely measured exposures. We attempted to minimize bias by the use of a highly structured questionnaire with questions about many different exposures. As neither subjects nor interviewers were aware of any specific study hypothesis, we expect reported usual intakes over the past year to be without recall bias or personality. Third, this model of research plainly compared the cases and controls for coffee consumption. Also,when considering the effect of coffee consumption, we did not consider the intake form, such as boiled, filtered, or instant coffee, or coffee type, such as caffeine or caffeine-free. Considering Koreans' habit of drinking coffee, served with sugar and creamer, this study's result and the actual influence of coffee could be different but insignificant. To overcome these limitations, there is a need for further study by prospective and cohort study of the relationship between coffee consumption and the possibility of inducing ischemic cerebral infarctions among the Korean population.

In summary, we concluded that coffee consumption was not a significant risk factor of ischemic cerebral infarction in Koreans.

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