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Poor nutrition and alcohol consumption are related to high serum homocysteine level at post-stroke

Seung-Hye Choi[1], Smi Choi-Kwon[2§], Min-Sun Kim[3] and Jong-Sung Kim[4]

[1]Department of Nursing Science, Suwon University, Gyeonggi 447-743, Korea
[2]College of Nursing & Research Institute of Nursing Science, Seoul National University, 103 Daehak-ro, Jongro-Gu, Seoul 110-799, Korea
[3]Nutritional Science, Department of Agriculture and Natural Resources, Michigan State University 48109, USA
[4]Neurology, Asan Medical Center, University of Ulsan College of Medicine, Seoul 138-736, Korea

BACKGROUND/OBJECTIVES: Increased serum homocysteine (Hcy) levels have been reported to be related to the occurrence of cardio- and cerebrovascular diseases. High serum Hcy levels are also related to the development of secondary stroke and all-cause mortality. The purpose of this study was to investigate the prevalence of high serum homocysteine level and relating factors, and the change over the 10 month period post-stroke.
SUBJECTS/METHODS: Consecutive stroke patients who were admitted to the Asan Medical Center were enrolled. Ten months after the onset of stroke, an interview with a structured questionnaire was performed and blood samples were obtained for the biochemical parameters. Nutritional status was determined using the mini nutritional assessment (MNA) score and dietary nutrient intakes were also obtained using a 24 hour recall method.
RESULTS: Out of 203 patients, 84% were malnourished or at risk of malnutrition, and 26% had high homocysteine levels at 10 months post-stroke. Using logistic regression, the factors related with high homocysteine levels at 10 months post-stroke included heavy alcohol consumption ($P = 0.020$), low MNA scores ($P = 0.026$), low serum vitamin B_{12} ($P = 0.021$) and low serum folate levels ($P = 0.003$). Of the 156 patients who had normal homocysteine levels at admission, 36 patients developed hyperhomocysteinemia 10 months post-stroke, which was related to heavy alcohol consumption ($P = 0.013$). Persistent hyperhomocysteinemia, observed in 22 patients (11%), was related to male sex ($P = 0.031$), old age ($P = 0.042$), low vitamin B_6 intake ($P = 0.029$), and heavy alcohol consumption ($P = 0.013$).
CONCLUSION: Hyperhomocysteinemia is common in post-stroke, and is related to malnutrition, heavy alcohol drinking and low serum level of folate and vitamin B_{12}. Strategies to prevent or manage high homocysteine levels should consider these factors.

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INTRODUCTION

Each year, about 105,000 Korean people experience a new or recurrent stroke, the estimated incidence is 216 per 100,000 person-years [1]. On average, every 5 minutes stroke attacks someone in Korea [1]. Stroke survivors are known to be at significantly increased risk for further strokes compared to the general population and the risk of stroke recurrence was reported to be about 11.1% at 1 year [2]. Increased serum homocysteine (Hcy) levels have been reported to be related to the occurrence of cardio- and cerebrovascular diseases [3]. High serum Hcy levels are also related to the development of secondary stroke and all-cause mortality [4]. However, many stroke patients continue to have elevated serum Hcy levels post-stroke [4]. Hyperhomocysteinemia was prevalent in about 20% of the patients with a history of stroke [5]. Malnutrition which is common in stroke patients [6,7] has been reported to be associated with high Hcy levels [8]. Low dietary vitamin intake was also reported to be a risk factor for high Hcy levels [9].

Although the effect of vitamin supplementation in reducing Hcy levels and preventing secondary stroke remains controversial [3,10,11] , and the effects of alcohol consumption on Hcy levels were contradictory [12,13], few studies have investigated relating factors to hyperhomocysteinemia, particularly so with regard to nutritional status and dietary intakes, and alcohol consumption in chronic stage stroke patient. Hence, in our present study we investigated the prevalence of high Hcy levels and relating factors at 10 months post-stroke in our patient cohort. We also investigated the Hcy changes over the 10 month period post-stroke and the factors related to those changes.

§ Corresponding Author: Smi Choi-Kwon, Tel. 82-2-740-8830, Fax. 82-2-765-4103, Email. smi@snu.ac.kr
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SUBJECTS AND METHODS

Study design

This was a parallel study of a previously published report [14] and consisted of a descriptive analysis of a stroke patient cohort at 10 months post-stroke. The institutional review board at the Asan Medical Center in Seoul, Korea, approved the study. All participants provided written informed consent when they were admitted to the hospital after stroke onset. Patient data (stroke sub type, NIHSS score, Hcy level at admission, and folate supplementation or warfarin administration) and the presence of risk factors, the lifestyle before stroke (drinking and smoking habits), and body mass index (BMI) at admission were obtained by a review of the medical records for each participant. Face-to-face interviews with the subjects as well as blood sample collections were performed at 10 months post-stroke at outpatient follow-up.

Patients

Consecutive stroke patients admitted to the Asan Medical Center between March 2008 and February, 2010 were enrolled in this study. The diagnosis of acute ischemic stroke was confirmed by diffusion weighted MRI (DWI) correlated with neurologic symptoms within 72 hours after stroke onset [10]. Exclusion criteria were: 1) intracerebral hemorrhage, subarachnoid hemorrhage, arteriovenous malformation, venous infarction or moyamoya disease; 2) transient ischemic attack without progression to a stroke; 3) communication problems (aphasia, dementia or dysarthria) that were severe enough to prevent a reliable interview; and 4) informed consent not given.

Data collection

Questionnaire survey

Interviews were performed by researchers at outpatient follow-ups at an average of 10 months (9-12 months) after the onset of stroke. The modified Rankin Scale (mRS) was recorded by an experienced stroke neurologist and categorized as severe (3-5) or mild (0-2) for statistical purposes. The National Institutes of Health Stroke Scale (NIHSS) which is a most commonly used tool for the assessment of neurological deficits post stroke [15] was also recorded by experienced stroke neurologist. NIHSS (ranges from 0 to 34) with high scores corresponding to increased severity of stroke with worse prognosis. To increase the inter-rater reliability of assessments, three formal training sessions were held prior to the interviews. Subsequently, each rater's initial interview session was supervised at the data collection site by one of the authors (S, C-K), and any disagreements were resolved by discussion. Questions that arose during subsequent interviews were brought to a research team meeting in order to reach consensus on the appropriate answer.

The questionnaire items included age, gender, current smoking behavior, current alcohol consumption, and perceived economic status. Current alcohol consumption was assessed from patient responses regarding amount, type, and frequency. This information was transformed into average grams of alcohol consumed per day [calculated by concentration of alcohol (%) $\times$ alcohol consumption (ml) $\times$ 0.78/100] [16]. For further analysis, each patient was classified as either a non-alcohol drinker, a moderate alcohol drinker (0.1-4.9 g/day), or a heavy drinker ($\geq$ 5 g/day) [17].

A retrospective review from the medical records of the subjects was undertaken to obtain body weight at admission and past alcohol consumption history.

Assessment of nutritional status and dietary intake

Nutritional status was evaluated using a mini nutritional assessment (MNA) scale [18] after outpatient interview. The MNA is a simple and accurate way to assess nutritional status in routine practice [19]; a higher MNA total score indicates a healthier nutritional status [19]. For statistical analysis, the patients were divided into three groups according to their MNA scores as follows: malnutrition (0-16.5 points), at risk of malnutrition (17-23.5 points), or well-nourished (24-30 points) [16]. To assess nutritional status, we also obtained BMI in addition to MNA score from the patients. BMI was calculated based on each participant's measured height and weight (kg/m^2) and was categorized as either non-obese ($\leq$ 25) or obese (> 25) [16,20]. Dietary intakes (calories, protein, dietary fiber, calcium, iron, vitamin A, vitamin E, vitamin B_6, vitamin C, and folate) were obtained using a 24 hour dietary recall method and were analyzed using a computer aided nutrition analysis program (CAN pro 3.0 version) [21].

One week before the visit to the outpatient clinic, phone calls were made to the patients to give instructions regarding the 24 hour dietary recall method. The patients received instructions to write down all of the foods and drinks that they consumed, including time and quantity, for two days (one weekday and one weekend day) and they were asked to bring these lists to their appointment. The 24 hour dietary recall was confirmed by means of face-to-face interview using a food model/portion-size booklet that included common Korean foods, utensils and portion sizes. The changes in the dietary patterns (meat, eggs, fishes, vegetables or fruits) after stroke were also investigated. The care-givers who accompanied the patients to the clinic verified the answers provided by the patients during the interview. When relatives were not present during the interview (n = 17, 8.37%), patient responses regarding smoking, drinking, and dietary intakes were confirmed by telephoning the relatives who lived with the patient.

Based on the obtained data from this analysis, average daily intakes of nutrients per person were determined according to recommended levels by the Dietary Reference Intakes for Koreans (KDRI's) [21]. Protein, calcium, iron, vitamin A, vitamin B_6, vitamin C, and folate intake deficiency were defined as less than 75% of the RNI (recommended nutrient intake) [21]. Dietary fiber and Vitamin E intake deficiency were defined as less than 75% of the AI (adequate intake) [21]. Calorie intake deficiency was defined as less than 75% of the EAR (estimated average requirement) [21].

Biochemistry

Blood samples were obtained from all patients after overnight fasting to obtain biochemical parameters [Hcy, hemoglobin (Hb), glucose, cholesterol, albumin, C-reactive protein (CRP),

transferrin, vitamin B_{12}, and folate, triglyceride (TG), high density lipoprotein (HDL), low density lipoprotein (LDL)]. Hyperhomocysteinemia was defined, when the concentration was higher than 15 μM/L in serum [22]. Hcy was measured by competitive immunoassay using ADIVA Centaur (Bayer).

Statistical analysis

General characteristics of the patients were tested using descriptive statistics. Related factors affecting Hcy levels at 10 months post-stroke were tested using the student's *t* test or the Chi-square test. Logistic regression was used to define the factors affecting Hcy levels at 10 months post-stroke. To investigate how Hcy level changes over time and what factors are related to the changes, we divided the normal homocysteinemia group at 10 months post stroke into the high to normal Hcy group (high at admission and normal at 10 months post stroke) and the persistently-normal group. We also subdivided the hyperhomocysteinemia group at 10 months post stroke into the normal to high Hcy group and the persistently-high Hcy group. They were analyzed using either the ANOVA test, or the Chi-square test. We also performed multivariable multinomial logistic regression to analyze the factors related to changing levels of Hcy. Changes in eating patterns after stoke with relation to the changes in Hcy levels were tested using the Chi-square test. Statistical significance was accepted at $P < 0.05$. Analyses were conducted using SPSS WIN 18.0 (SPSS Inc., Chicago, IL).

RESULTS

Characteristics of subjects

Of the 550 stroke patients admitted to our hospital during the defined time period in this study, 298 patients [n = 283 (95%) transferred to local hospitals near the patients' residential area; and n = 15 (4%) changed their contact numbers] could not be followed at 10 months post-stroke, which left 252 patients eligible for our analysis. In terms of demographics, stroke severity on admission, and the presence of risk factors, there were no significant differences between the patients who were followed and the patients who were not (data not shown). Of the 252 eligible patients, 49 dropped out, leaving a cohort of 203 patients at 10 months post-stroke for analysis. The subjects who dropped out included 8 patients with deteriorating physical conditions, 2 patients with dementia, 33 patients who refused to take blood samples, and 6 patients who had died (Fig. 1).

Biological variables and related factors according to Hcy levels at 10 months post-stroke

Forty-seven patients (23.2%) had hyperhomocysteinemia at admission and 58 patients (28.6%) had hyperhomocysteinemia at 10 months post-stroke. Malnutrition was present in 15 patients (7.7%), and 149 patients (76%) were at risk of malnutrition at 10 month post-stroke (Table 1). Deficiency in folate intake occurred in 88.7% of the patients (Table 1). Factors related to high Hcy levels at 10 months post-stroke included old age ($P = 0.021$), male sex ($P = 0.009$), previous alcohol consumption before the stroke ($P = 0.023$), current alcohol consumption ($P = 0.003$), current smoking ($P = 0.040$), high Hb ($P = 0.042$), low serum vitamin B_{12} ($P = 0.011$), and low serum folate ($P = 0.002$) (Table 1). The MNA score was significantly lower in the high Hcy group than in the normal Hcy group ($P = 0.045$) (Table 1).

Among the patients with malnutrition or who were at risk of malnutrition, 33.7% (n = 55) were obese (Table 2). The caloric intake was lower in the patients with the malnutrition or at risk of malnutrition than in the patients with well-nourished ($P = 0.036$) (Table 2).

The variables that were associated with hyperhomocysteinemia at 10 months post-stroke in the univariate analysis (potentially confounding variables such as gender or age) were included in the regression model. By logistic regression analysis, the factors that were independently related to high Hcy levels at 10 months post-stroke included current alcohol consumption ($P = 0.020$), low MNA score ($P = 0.026$), low serum vitamin B_{12} ($P = 0.021$) and folate levels ($P = 0.003$) (Table 3).

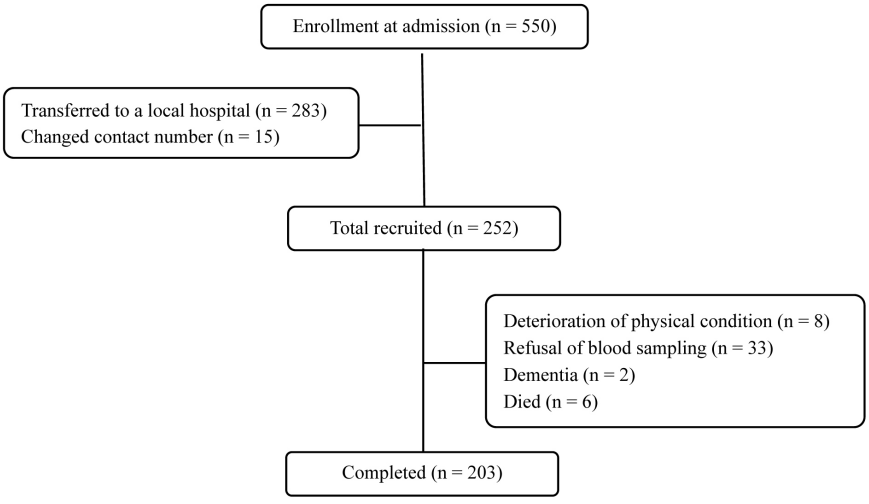

Fig. 1. Recruitment flow chart

Table 1. Biological variables and related factors according to Homocysteine levels at 10 months post-stroke (n = 203)

	Total	Normal group	High group	t or χ^2	*P*-value
	n = 203 (100.0) Mean ± SD or No (%)	n = 145(71.4) Mean ± SD or No (%)	n = 58(28.6) Mean ± SD or No (%)		
Age (yrs)	60.03 ± 12.11	58.83 ± 12.28	63.03 ± 11.22	-2.348	0.021
Gender (M)	133 (65.5)	87 (60.0)	46 (79.3)	6.838	0.009
Stroke type					
Ischemic	125 (63.8)	84 (60.0)	41 (73.2)	3.464	0.326
Hemorrhagic	11 (5.6)	8 (5.7)	3 (5.4)		
Single sub cortical-infarct	60 (30.6)	48 (34.3)	12 (21.4)		
Economic status					
Very low	24 (12.3)	18 (12.8)	6 (11.1)	0.415	0.937
Low	45 (23.1)	31 (22.0)	14 (25.9)		
Moderate	65 (33.3)	47 (33.3)	18 (33.3)		
High	61 (31.3)	45 (31.9)	16 (29.6)		
Previous alcohol consumption (g/day)	1.71 ± 3.48	1.36 ± 2.78	2.58 ± 4.72	-2.287	0.023
Non-drinker	118 (58.1)	91 (62.8)	27 (46.6)	4.687	0.096
Moderate-drinker	60 (29.6)	39 (26.9)	21 (36.2)		
Heavy-drinker	25 (12.3)	15 (10.3)	10 (17.2)		
Current alcohol consumption (g/day)	0.23 ± 1.08	0.09 ± 0.45	0.58 ± 1.85	-1.993	0.003
Non-drinker	171 (85.5)	124 (87.0)	47 (81.0)	9.996	0.007
Moderate-drinker	25 (12.5)	18 (12.7)	7 (12.1)		
Heavy-drinker	4 (2.0)	0 (.0)	4 (6.9)		
Current Smoking (yes)	82 (40.4)	54 (37.2)	28 (48.3)	6.420	0.040
mRS at 10 months post stroke	0.97 ± 0.99	0.93 ± 0.92	1.09 ± 1.14	-1.029	0.305
Mild(0-2)	178 (90.8)	131 (92.9)	47 (85.5)	2.635	0.165
Severe(3-5)	18 (9.2)	10 (7.1)	8 (14.5)		
NIHSS score at 10 months post stroke	1.53 ± 2.04	1.45 ± 1.90	1.70 ± 2.40	-0.763	0.447
BMI (kg/m^2)	24.28 ± 3.12	24.48 ± 3.14	23.77 ± 3.03	1.439	0.152
Obese (yes)	70 (35.9)	55 (39.0)	15 (27.8)	2.140	0.182
Hypertension(yes)	138 (68.0)	93 (64.1)	45 (77.6)	3.442	0.064
Diabetes(yes)	49 (24.1)	34 (23.4)	15 (25.9)	0.132	0.423
Biochemical data					
Hb (g/dl)	14.16 ± 1.56	14.02 ± 1.49	14.51 ± 1.66	-2.043	0.042
Glucose (mg/dl)	109.49 ± 29.98	108.75 ± 25.19	111.34 ± 36.99	-0.575	0.566
Cholesterol (mg/dl)	159.43 ± 34.07	159.35 ± 35.35	159.64 ± 27.87	-0.575	0.957
Albumin (g/dl)	4.22 ± 0.30	4.21 ± 0.27	4.22 ± 0.36	-0.111	0.912
CRP (mg/dl)	0.16 ± 0.27	0.16 ± 0.30	0.15 ± 0.18	0.441	0.659
Transferrin (mg/dl)	253.14 ± 46.93	253.43 ± 46.77	252.41 ± 47.71	0.140	0.889
Vitamin B_{12} (pg/ml)	633.56 ± 249.58	661.77 ± 267.89	563.03 ± 179.92	2.582	0.011
Folate (ng/ml)	10.21 ± 7.34	11.19 ± 7.49	7.76 ± 6.41	3.070	0.002
TG (mg/dl)	121.96 ± 62.97	117.92 ± 62.94	132.03 ± 62.42	-1.446	0.150
HDL (mg/dl)	50.38 ± 12.21	51.10 ± 12.95	48.59 ± 10.01	1.329	0.185
LDL (mg/dl)	92.47 ± 27.81	92.41 ± 29.01	92.62 ± 24.79	-0.048	0.962
Folate supplement (yes)	6 (5.3)	5 (6.4)	1 (2.9)	0.607	0.394
Warfarin supplement (yes)	19 (16.7)	11 (13.8)	8 (22.9)	1.464	0.277
MNA score	21.17 ± 2.87	21.42 ± 2.60	20.51 ± 3.40	2.017	0.045
Nutritional Status					
Malnutrition	15 (7.7)	8 (5.7)	7 (12.7)	3.948	0.139
Risk for malnutrition	149 (76.0)	107 (75.9)	42 (76.4)		
Normal	32 (16.3)	26 (18.4)	6 (10.9)		
Nutrient deficiency (yes)					
Calorie (kcal)	167 (82.3)	116 (80.0)	51 (87.9)	1.786	0.181
Protein (g)	71 (35.0)	48 (33.1)	23 (39.7)	0.782	0.377
Dietary fiber (g)	148 (72.9)	104 (71.7)	44 (75.9)	0.359	0.549

Table 1. continued

	Total	Normal group	High group	*t*	*P*-value
	n = 203 (100.0) Mean ± SD or No (%)	n = 145(71.4) Mean ± SD or No (%)	n = 58(28.6) Mean ± SD or No (%)		
Calcium (mg)	177 (87.2)	124 (85.5)	53 (91.4)	1.275	0.259
Iron (mg)	50 (24.6)	33 (22.8)	17 (29.3)	0.958	0.328
Vitamin A (μgRE)	146 (71.9)	102 (70.3)	44 (75.9)	0.624	0.429
Vitamin E (mg)	99 (48.8)	70 (48.3)	29 (50.0)	0.049	0.824
Vitamin B_6 (mg)	61 (30.0)	39 (26.9)	22 (37.9)	2.400	0.121
Vitamin C (mg)	130 (64.0)	94 (64.8)	36 (62.1)	0.137	0.711
Folate (μg)	180 (88.7)	127 (87.6)	53 (91.4)	0.593	0.441

M, male; SD, standard deviation; mRS, modified rankin score; NIHSS, National Institute health stroke scale; BMI, body mass index; Hb, hemoglobin; CRP, C-reactive protein; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MNA, mini nutritional assessment

Table 2. Changes in nutritional status after stroke

Variables	Malnutrition or risk of malnutrition group	Normal group	*t* or χ^2	*P*-value
	n = 164 (83.7%) Mean ± SD or no (%)	n = 32 (16.3%) Mean ± SD or no (%)		
Obese (yes)	55 (33.7)	15 (46.9)	2.005	0.113
Weight change after stroke onset			5.048	0.028
Decreased more than 3kg	41 (26.8)	2 (7.1)		
Increased or not changed	112 (73.2)	29 (92.9)		
Caloric intake (kcal)	1,431.33 ± 466.71	1,618.35 ± 413.40	-2.110	0.036

Table 3. Factors affecting Homocysteine levels at 10 months post-stroke

Variables	B	S.E.	*P*-value[1)]	Adjusted OR	95% CI	
Current alcohol consumption (g/day)	0.758	0.325	0.020	2.133	1.127	4.036
MNA scores	-0.271	0.122	0.026	0.762	0.600	0.968
Serum vitamin B_{12} (pg/ml)	-0.003	0.001	0.021	0.997	0.994	0.999
Serum folate (ng/ml)	-0.207	0.069	0.003	0.813	0.710	0.932

OR, odds ratio; CI, confidence limits; MNA, mini nutritional assessment
Adjusted for age, gender, previous alcohol consumption, current smoking, hemoglobin
[1)] *P*-value by multiple logistic regression

Table 4. Factors related to changing levels of Homocysteine at 10 months post-stroke (n = 203)

	Normal group (n = 145, 71.4%)		High group (n = 58, 28.6%)		χ^2	*P*-value
	High to normal n = 25 (12.3%)	Persistently normal n = 120 (59.1%)	Normal to high n = 36 (17.7%)	Persistently high n = 22 (10.9%)		
Gender (M)	18 (72.0)	69 (57.5)	28 (77.8)	19 (81.8)	8.862	0.031
Age (yrs)	55.96 ± 12.65	59.43 ± 12.18	61.61 ± 11.81	65.36 ± 10.00	2.736	0.045
MNA scores	20.52 ± 3.21	21.62 ± 2.42	20.46 ± 3.67	20.60 ± 2.95	2.398	0.069
Obese (yes)	10 (40.0)	45 (38.8)	8 (22.9)	7 (36.8)	3.199	0.362
Nutrient deficiency (yes)						
Calorie	23 (92.0)	93 (77.5)	29 (80.6)	22 (100.0)	8.307	0.040
Protein	10 (40.0)	38 (31.7)	12 (33.3)	11 (50.0)	3.082	0.379
Dietary fiber	14 (56.0)	90 (75.0)	25 (69.4)	19 (86.4)	6.119	0.106
Calcium	22 (88.0)	102 (85.0)	31 (86.1)	22 (100.0)	3.800	0.284
Iron	7 (28.0)	26 (21.7)	8 (22.2)	9 (40.9)	3.974	0.264
Vitamin A	16 (64.0)	86 (71.7)	27 (75.0)	17 (77.3)	1.262	0.738
Vitamin E	15 (60.0)	55 (45.8)	16 (44.4)	13 (59.1)	2.884	0.410
Vitamin B_6	8 (32.0)	31 (25.8)	10 (27.8)	12 (54.5)	7.429	0.059
Vitamin C	16 (64.0)	78 (65.0)	19 (52.8)	17 (77.3)	3.704	0.295
Folate	20 (80.0)	107 (89.2)	32 (88.9)	21 (95.5)	2.910	0.406
Alcohol-consumption before the stroke (g/day)	1.41 ± 1.74	1.35 ± 2.95	2.67 ± 5.27	1.71 ± 3.48	1.751	0.158
Current alcohol-consumption (g/day)	0.01 ± 0.03	0.11 ± 0.49	0.62 ± 1.72	0.52 ± 2.09	2.991	0.032

M, male; MNA, mini nutritional assessment

Table 5. Multinomial logistic regression model for related factors to changing levels of Homocysteine at 10 months post-stroke (n = 203)

Variables	Normal vs. High to normal			Normal vs. Normal to high			Normal vs. persistently high		
	Adjusted OR	95% CI	*P*-value[1)]	Adjusted OR	95% CI	*P*-value[1)]	Adjusted OR	95% CI	*P*-value[1)]
Calorie intake (kcal)	0.999	0.998-1.000	0.130	1.000	0.999-1.001	0.759	0.998	0.996-0.999	0.002
Current alcohol-consumption (g/day)	0.005	405.1-536.5	0.367	1.538	1.006-2.353	0.047	1.492	0.935-2.381	0.093

OR, odds ratio; CI, confidence limits
Adjusted for age, gender
[1)] *P*-value by multinomial logistic regression

Table 6. Changes in eating patterns after stroke according to the changes in Homocysteine levels at 10 months post-stroke (n = 203)

		Normal group		High group		χ^2	*P*-value
		High to normal n = 25 (12.3%)	Persistently normal n = 120 (59.1%)	Normal to high n = 36 (17.7%)	Persistently high n = 22 (10.9%)		
Total food intake	Less	13 (52.0)	62 (51.7)	21 (58.3)	13 (59.1)	0.977	0.986
	Same	11 (44.0)	52 (43.3)	13 (36.1)	8 (36.4)		
	More	1 (4.0)	6 (5.0)	2 (5.6)	1 (4.5)		
Grains or starch intake	Less	10 (40.0)	51 (42.5)	17 (47.2)	9 (42.9)	0.776	0.993
	Same	14 (56.0)	66 (55.0)	18 (50.0)	11 (52.4)		
	More	1 (4.0)	3 (2.5)	1 (2.8)	1 (4.8)		
Vegetable or fruit intake	Less	4 (16.0)	14 (11.9)	4 (11.1)	2 (9.5)	12.529	0.185
	Same	17 (68.0)	66 (55.9)	20 (55.6)	15 (71.4)		
	More	3 (12.0)	38 (32.2)	12 (33.3)	4 (19.0)		
Milk or dairy intake	Less	2 (8.0)	12 (10.0)	4 (11.1)	4 (19.0)	5.058	0.536
	Same	21 (84.0)	85 (70.8)	28 (77.8)	15 (71.4)		
	More	2 (8.0)	23 (19.2)	4 (11.1)	2 (9.5)		
Oil or fat intake	Less	9 (36.0)	55 (45.8)	17 (47.2)	9 (42.9)	1.986	0.921
	Same	15 (60.0)	63 (52.5)	18 (50.0)	12 (57.1)		
	More	1 (4.0)	2 (1.7)	1 (2.8)	0 (0.0)		

Factors related to changing levels of Hcy at 10 months post-stroke

We categorized the patients into four groups according to the changes in Hcy levels between stroke onset and 10 months post-stroke [the high to normal Hcy group (n = 25), persistently normal group (n = 120), the normal to high Hcy group (n = 36), and the persistently high Hcy group (n = 22)]. Male sex (P = 0.031), old age (P = 0.045), and calorie deficiency (P = 0.040) were more common in the persistently high Hcy group than the other three groups. Current alcohol consumption was more common in the normal to high group than the other three groups (P = 0.032) (Table 4).

In order to investigate the predicting factors to the changing levels of Hcy, a multinomial logistic regression was performed. By selecting the persistently normal group as the reference group, the high to normal Hcy group, the normal to high Hcy group, and the persistently high Hcy group were compared to the reference group. When controlling for age and gender, the current alcohol consumption (P = 0.047) was a significant predictor for the normal to high Hcy group (Table 5). When controlling for age and gender, the low caloric intake (P = 0.002) was a significant predictor for the persistently high group (Table 5). There were no significant changes in eating patterns after stroke in the four groups (Table 6).

DISCUSSION

In this study, we assessed Hcy level at 10 months post-stroke, and attempted to elucidate factors related to high Hcy such as lifestyle, nutritional status and dietary intake of nutrients. We found that the prevalence of hyperhomocysteinemia (> 15 μmol/L) at 10 months post-stroke (28.6%) was comparable to that at admission (23.2%). The prevalence of high Hcy levels in our patients was slightly lower than that observed in a previous study (34%) that evaluated elderly stroke survivors (1.5 years post-stroke) [22]. Because old age was found to be a risk factor for high Hcy levels in our present study, the younger mean age of our patient population may have resulted in a relatively low prevalence of high Hcy levels.

We found that 83.7% of our patients had either malnutrition or were at risk of malnutrition [7]. We were surprised by the high percentages of the patients with either malnutrition or malnurtition at risk since 90% of our subjects had a mild stroke (mRS 0-2). It may have been due to the weight loss in these patients after stroke. We found that the patients with malnutrition or risk of malnutrition had more weight loss over the 10 months period than those who had normal nutritional status (P = 0.028). We also evidenced that the lower mean energy intake in the patients with malnutrition or risk of malnutrition than in patients with normal nutritional status (P = 0.036). This is similar to the result of a previous study (81%) carried out at 6 months post-stroke [23].

We found that a low MNA score (P = 0.045) was a factor related to hyperhomocysteinemia, supporting a positive relationship between poor nutritional status and hyperhomocysteinemia [24]. It remains unclear why patients with poor nutritional status develop hyperhomocysteinemia. It is possible that an

increase in total Hcy may be the result of a malnourished body attempting to preserve methionine homeostasis [25]. In addition, among our patients with malnutrition or at risk of malnutrition 33.7% (n = 55) were obese and consumed animal protein ($P = 0.024$) and folate ($P = 0.030$) insufficiently as compared with non-obese patients (data not shown). It, therefore, is possible that these patients may have reduced the intake of all foods, including meat and vegetables, thereby consuming insufficient amounts of folate.

Upon further analysis, patients with low MNA were older ($P = 0.022$) and had higher mRS ($P = 0.029$), lower caloric intake ($P = 0.026$), lower animal protein intake ($P = 0.066$), and lower lipid intake ($P = 0.041$) compared with those with high MNA scores (> 23, the well-nourished group) (data not shown). Considering that poor nutritional status is also related to poor recovery and increased mortality in stroke patients [7], special attention should be given to patients with poor nutrition.

In our study, heavy alcohol consumption was a factor independently related to a high Hcy level at 10 months post-stroke, despite the fact that our subjects reported that they had reduced alcohol consumption after stroke onset. Upon further analysis, the current alcohol consumption ($P = 0.047$) was a significant predictor for the normal to high Hcy group compared with the persistently normal group.

Heavy alcohol consumption being a risk factor for high homocysteinemia is not consistent with the findings of a previous study, which reported the beneficial effects of alcohol consumption on decreasing serum Hcy levels [26]. The discrepancy between our data and those of previous study [26] might have been due to the different amount or type of alcohol consumed [27,28]. Traditionally, Koreans drink distilled alcohol called 'Soju', which does not contain folate or vitamins.

The positive relationship between heavy alcohol consumption and high Hcy levels may be due to the fact that heavy alcohol consumption reduces folate absorption by inhibiting the methionine synthase enzyme [29]. Since decreased folate absorption by heavy alcohol consumption may be overcome by sufficient folate intake [29], folate therapy may be needed in patients who consume certain types of alcohol heavily.

Consistent with the data from a previous study [30], in our study, low serum vitamin B_{12} ($P = 0.021$), and folate levels ($P = 0.003$) were closely related to hyperhomocysteinemia. However, in our study, dietary folate intake was not related to Hcy levels. Because folate deficiency was common (88.7%) among our study subjects, the effect of dietary folate intake could have been masked. Alternatively, it may also be related to the fact that serum folate levels are not affected by dietary inadequacy alone, but also by intestinal malabsorption, altered hepatobiliary metabolism, and increased renal excretion [31]. Indeed, a previous study reported inconsistent results on the relationship between folate intake and serum folate levels [32]. Due to the low bioavailability of dietary folic acid, at least 500 μg of folic acid taken daily are required to treat hyperhomocysteinemia [9]. However, we found that the average daily folate intake in our subjects was 266 μg, far less than the reported requirement [22]. Because of low costs and safety of the therapy, American Heart and Stroke Association advises to treat stroke and hyperhomocysteineima patients daily with 0.4mg folic acid, 2.4 μg B_{12} vitamin and 1.7 mg B_6 vitamin, although significant benefit in secondary prevention is not yet proven [12]. Further studies are warranted to understand the efficacy of folate intake in patients at high risk for hyperhomocysteinemia, which includes those who drink alcohol or are malnourished.

Our study has several limitations. First, we were unable to contact 20% of the admitted patients by phone for the 10 month follow-up. Most of our study patients live in Seoul, Korea, which is a metropolitan city with many people changing their addresses for various reasons, making it sometimes difficult to locate them. However, mRS scores and socio-demographic data were not significantly different between the patients who were followed (n = 203) and those who were not at 10 months post-stroke (n = 347). Therefore, the resultant sampling bias may not be significant. Secondly, the nutritional status in our cohort was determined by MNA score, which is a screening tool for the elderly population. However, MNA total scores (0-30 points) have been reported to be correlated with caloric and nutrient intakes, as well as anthropometric and biological nutritional parameters [33]. In our present study we also determined obesity using BMI to supplement MNA scores.

In conclusion, we have found that a high Hcy is common in post-stroke patients. Post-stroke nutritional education programs should therefore emphasize to maintain good nutritional status with adequate dietary intake of nutrients such as calories and animal proteins. Patients who drink alcohol should also be advised to limit alcohol consumption and, if possible, to cautiously select the type of alcohol they consume.

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