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SCIENCE DIRECT
Metabolism Clinical and Experimental 55 (2006) 656–661
Metabolism
Clinical and Experimental
www.elsevier.com/locate/metabol

Hyperhomocysteinemia is a significant risk factor for silent cerebral infarction in patients with chronic renal failure undergoing hemodialysis

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Received 1 October 2005; accepted 3 December 2005

Abstract

In patients with chronic renal failure undergoing hemodialysis (HD), the presence of silent cerebral infarction (SCI) is associated with high mortality. Plasma total homocysteine (tHcy), which increases with renal dysfunction, has been flagged as a novel predictor for cerebrovascular events. We tested the hypothesis that the presence of SCI correlates with tHcy in HD patients. Based on brain magnetic resonance imaging findings, 44 patients undergoing HD were divided into a with-SCI group (61 ± 9 years [mean ± SD]; n = 24) and a without-SCI group (60 ± 8 years, n = 20), in whom 24-hour ambulatory blood pressure monitoring was performed. The number of patients with diabetes or hypertension was not different between the 2 groups. We made the following observations: (1) the percentage of smokers was higher in the with-SCI group than in the without-SCI group ($P < .05$); (2) plasma levels of high-density lipoprotein cholesterol were lower and tHcy was higher in the with-SCI group than in the without-SCI group ($P < .05$ and $P < .0001$, respectively); (3) and systolic ambulatory blood pressure and mean heart rate during nighttime were higher in the with-SCI group than in the without-SCI group ($P < .05$). Multivariate logistic analysis identified hyperhomocysteinemia as an independent and significant risk factor for SCI (odds ratio, 1.22; 95% CI, 1.10-1.36; $P < .01$). Our findings indicate that plasma tHcy may be a novel useful predictor for SCI in patients with chronic renal failure undergoing HD.

1. Introduction

The mortality in chronic hemodialysis (HD) patients related to cerebrovascular events is 4 to 10 times higher compared with the general populations [1].

Strokes in HD patients are characterized by the high rate of intracerebral hemorrhage, and hypertension is also a significant risk factor for stroke in this group [2-5]. Silent cerebral infarction (SCI) is thought to be an underlying or concomitant condition of clinical subcortical brain infarction or brain hemorrhage [6]. In most cases, SCI is found as a lacunar infarction, the most common form of subcortical infarction, defined by Fisher [7] as small, deep cerebral infarction caused by occlusion of small penetrating cerebral arteries. The incidence of SCI has been reported to be 2.5 to 4.5 times [8] higher in hyperhomocysteinemia, which is an independent risk factor for vascular diseases, such as cerebrovascular and cardiovascular diseases [9,10].

The significance of increased plasma total homocysteine (tHcy) with SCI in HD patients has not been adequately investigated. We hypothesized that increased levels of tHcy are associated with SCI in HD patients. To test our hypothesis, we compared in the present study the magnetic

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doi:10.1016/j.metabol.2005.12.007

resonance imaging (MRI), 24-hour ambulatory blood pressure monitoring, echocardiography, metabolic profiles, and smoking habits in Japanese HD patients with SCI and those without SCI, followed by evaluation of the independent predictors of SCI in these patients.

2. Subjects and methods

2.1. Patients

A total of 44 patients on HD (age, 61 ± 8 years [mean ± SD]; 25 men and 19 women) who were admitted to our hospital between 2002 and 2004 were enrolled in this study. The clinical characteristics of the studied patients are summarized in Table 1. All HD patients received regular dialysis using a high-flux cellulose triacetate or polysulfone hollow-fiber dialyzer 3 times per week in sessions lasting 4 hours. The dialysate flow rate was 500 mL/min, and blood flow ranged from 120 to 200 mL/min. The dry weight was determined for each patient based on the post-HD cardiothoracic ratio, clinical observations such as presence of muscle cramps, general fatigue, thirst, or hypotension during the HD session, and all patients were maintained at their set dry weight. No difference was recognized between the 2 groups with respect to dialysis methods. Patients with atrial fibrillation, liver dysfunction, or a history of symptomatic stroke, transient ischemic attacks, or dementia; autosomal-dominant polycystic kidneys; chronic infection; chronic inflammatory disease; or malignant disease were excluded from the study. All subjects gave their written informed consent to participate in the study, and the study protocol was approved by the ethics committee of the Oita Red Cross Hospital.

Table 1
Clinical characteristics of studied patients

	SCI (−)	SCI (+)	*P*
Age (y)	60 ± 8	61 ± 9	NS
Sex (male/female)	11/9	14/10	NS
Body mass index (kg/m^2)	22.1 ± 2.2	22.7 ± 2.5	NS
Dialysis duration (y)	1.7 ± 1.3	1.9 ± 1.5	NS
Diabetes mellitus (%)	55	63	NS
Hypertension (%)	75	83	NS
Dyslipidemia (%)	45	54	NS
Smoking habit (%)	15	46	.0288
IHD (%)	10	38	.0359
Drug use (%)			
Sulfonylurea	30	33	NS
α-Glucosidase inhibitors	25	21	NS
Insulin	10	13	NS
Statin	40	43	NS
Calcium channel antagonists	65	71	NS
ACE inhibitors	10	17	NS
Angiotensin receptor blocker	20	29	NS
β-blocker	15	17	NS
Hematocrit (%)	30.2 ± 3.6	29.6 ± 3.1	NS
Total cholesterol (mg/dL)	157 ± 60	172 ± 64	NS
Triglyceride (mg/dL)	102 ± 31	114 ± 42	NS
HDL-C (mg/dL)	46 ± 14	37 ± 11	.0272
Fasting plasma glucose (mg/dL)	129 ± 22	132 ± 27	NS
Hemoglobin A_{1c} (%)	6.3 ± 0.9	6.5 ± 1.3	NS
Uric acid (mg/dL)	6.8 ± 1.8	8.1 ± 2.3	.0461

Data are expressed as mean ± SD. ACE indicates angiotensin-converting enzyme; NS, not significant.

2.2. Risk factors

To evaluate risk factors, we investigated the presence or absence of hypertension, diabetes mellitus, dyslipidemia, ischemic heart disease (IHD), and smoking. Hypertension was defined as a mean 24-hour systolic ambulatory blood pressure (sABP) greater than 135 mm Hg or mean 24-hour diastolic ABP (dABP) greater than 85 mm Hg [11], or if the subject was being treated with antihypertensive drugs. Diabetes mellitus was designated as present if patients were using insulin or oral hypoglycemic agents or if the fasting glucose concentration was greater than 126 mg/dL. Twenty of twenty-four with-SCI patients and 15 of 20 without-SCI patients met this criterion, and all of these patients were being treated with calcium channel antagonists, β-blockers, angiotensin-converting enzyme inhibitors, and/or angiotensin II receptor blockers. Dyslipidemia was defined as fasting triglycerides of 200 mg/dL or greater, or high-density lipoprotein cholesterol (HDL-C) of less than 45 mg/dL for women and less than 35 mg/dL for men [12], or patients who were receiving medical treatment of hyperlipidemia. Ischemic heart disease was defined as either angina, history of myocardial infarction, coronary artery bypass surgery, or percutaneous coronary intervention. Smoking was defined as current cigarette smokers.

In HD patients, blood samples were taken from the arterial line before HD sessions.

Serum from blood samples was separated and stored at −20°C until assayed. Serum tHcy level was determined using the homocysteine microplate enzyme immunoassay assay (Bio-Rad Laboratories, Oslo, Norway) [13,14]. The within- and between-assay imprecision is less than 6% and less than 8%, respectively, and results using this method showed good correlation with those obtained by high-pressure liquid chromatography [13,14].

2.3. Twenty-four–hour ABP monitoring

During admission, 24-hour ABP was measured by the cuff-oscillometric method using an ABP monitoring system (TM-2425, A&D, Tokyo, Japan) with carbon dioxide gas–powered cuff inflation. The accuracy of these devices was previously validated [15]. The ABP monitors were placed at the end of the dialysis treatment in a midweek period. Blood pressure was measured every 30 minutes from 6:00 AM to 10:00 PM, and every 60 minutes from 10:00 PM to 6:00 AM of the following day [16,17]. Blood pressure was obtained as the mean value during the awake period between 6:00 AM and 10:00 PM and during the sleep period between 10:00 PM and 6:00 AM, respectively [16,17]. The waking time, time of falling asleep, and quality of sleep were assessed by interview with each patient. Patients who complained of sleep disturbance during ABP monitoring were excluded

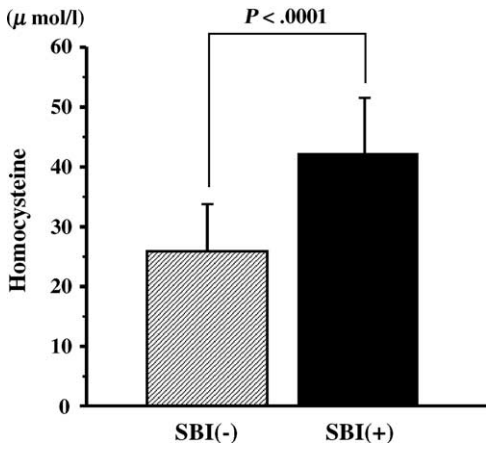

Fig. 1. Comparison of plasma tHcy between HD patients with SCI (+) and those without SCI (−). Data represent mean ± SD.

from analysis. Subjects whose mean nighttime sABP fell by more than 10% compared with their mean day-time sABP value were defined as dippers. The remaining subjects were defined as nondippers [18].

2.4. Echocardiography

M-mode 2-dimensional echocardiography and cardiac Doppler recordings were obtained by means of a phase-array echo-Doppler system. Echocardiograms were obtained in a standard manner using standard parasternal, short-axis, and apical views. Left ventricular mass was calculated as described previously [19]: left ventricular mass = $\{1.04 [(LVID_d + IVST_d + PWT_d]^3 - LVID_d^3) - 14 g\}$, where $LVID_d$ is the left ventricular internal dimension at end diastole; $IVST_d$, intraventricular septal thickness at end diastole; and PWT_d, posterior wall thickness at end diastole. Left ventricular mass was divided by body surface area to calculate the left ventricular mass index (LVMI). Pulsed Doppler recordings were made from the standard apical 4-chamber view. Mitral inflow velocity was recorded with the sample volume at the mitral annulus level; the average of ≥3 cardiac cycles taken. The following measurements were made: peak velocity of early ventricular filling (E), peak velocity of late ventricular filling (A), and their ratio (E/A) and deceleration time.

2.5. Evaluation of SCI

All participating patients had a brain MRI that used a superconducting magnet at a field of 1.5 T on proton density, T1-, and T2-weighted images in axial planes at 5-mm-thick slices. Lacunar infarction was defined as the presence of a hyperintense area on T2-weighted images (5 mm ≤ diameter < 15 mm) that was visible as a low-signal intensity on T1-weighted images. To exclude enlarged periventricular spaces, lesions less than 5 mm were not counted as infarctions, as described by Braffman et al [20]. The magnetic resonance images were assessed independently by 2 neurologists.

2.6. Statistical analysis

All data are presented as mean ± SD. Differences between groups were examined with Student t test. Categorical variables were compared using χ^2 analysis. Multiple logistic regression analysis was used to assess the combined influence of variables on SCI. Sex, hypertension, diabetes mellitus, dyslipidemia, IHD, smoking, and nondippers were represented by dummy variables (1 = male, 0 = female; 1 = presence, 0 = absence) in logistic regression analysis. A model selection procedure was used to select the simplest regression model, that is, to decide significant risk factors. A value of $P < .05$ was considered statistically significant.

3. Results

As demonstrated in Table 1, the mean age was similar between the with-SCI group and the without-SCI group. No significant differences were observed between the 2 groups with respect to sex, body mass index, or HD duration. The percentages of patients with diabetes, hypertension, dyslipidemia, and administered medications were similar between the 2 groups. However, the percentages with smoking habit and IHD were higher in the with-SCI group than in the without-SCI group ($P = .0288$ and $P = .0359$, respectively).

There was no significant difference in hematocrit, fasting plasma glucose concentration, and hemoglobin A_{1c}. With regard to lipid metabolism, serum HDL-C was lower in the with-SCI group than in the without-SCI group ($P = .0272$), whereas serum total cholesterol and triglyceride showed no significant difference between the groups. Uric acid was higher in the with-SCI group than in the without-SCI group ($P = .0461$).

Table 2
Ambulatory blood pressure monitoring findings

	SCI (−)	SCI (+)	P
24 h			
Systolic ambulatory blood pressure (mm Hg)	136 ± 6	139 ± 11	NS
Diastolic ambulatory blood pressure (mm Hg)	78 ± 9	77 ± 10	NS
Heart rate (beats/min)	70 ± 6	71 ± 5	NS
Daytime			
Systolic ambulatory blood pressure (mm Hg)	141 ± 7	143 ± 11	NS
Diastolic ambulatory blood pressure (mm Hg)	81 ± 9	79 ± 11	NS
Heart rate (beats/min)	73 ± 6	74 ± 6	NS
Nighttime			
Systolic ambulatory blood pressure (mm Hg)	124 ± 7	132 ± 13	.0158
Diastolic ambulatory blood pressure (mm Hg)	68 ± 8	71 ± 10	NS
Heart rate (beats/min)	61 ± 5	65 ± 5	.0172
Nondippers (%)	45	75	.0419

Data are expressed as mean ± SD.

Table 3
Echocardiographic findings

	SCI (−)	SCI (+)	*P*
Ejection fraction (%)	63 ± 7	62 ± 9	NS
$LVID_d$ (mm)	46 ± 3	47 ± 4	NS
$LVID_s$ (mm)	32 ± 4	33 ± 5	NS
$IVST_d$ (mm)	9.8 ± 1.9	10.7 ± 1.4	NS
PWT_d (mm)	10.0 ± 1.5	11.1 ± 1.6	.0256
LVMI (g/m^2)	127 ± 30	151 ± 41	.0375
E/*A* ratio	0.83 ± 0.12	0.74 ± 0.16	.0458
Deceleration time (ms)	258 ± 32	276 ± 30	NS

Data are expressed as mean ± SD. $LVID_d$ indicates left ventricular internal dimension at end diastole; $LVID_s$, left ventricular internal dimension at end systole; $IVST_d$, interventricular septal thickness at end diastole; PWT_d, posterior wall thickness at end diastole.

Fig. 1 shows tHcy in the with-SCI and without-SCI groups of HD patients. Total homocysteine was higher in the with-SCI group than in the without-SCI group (42.5 ± 9.2 vs 26.0 ± 7.8 μmol/L, $P < .0001$).

The ABP data are shown in Table 2. sABP, dABP, and heart rate during the day were similar between the groups. In contrast, nighttime sABP and heart rate were higher in the with-SCI group than in the without-SCI group ($P = .0158$ and $P = .0172$, respectively). However, nighttime dABP was similar between the 2 groups. The 24-hour mean sABP, dABP, and heart rate were similar in the 2 groups. The percentage of nondippers was higher in the with-SCI group than in the without-SCI group ($P = .0419$).

Table 4
Univariate logistic regression analysis with silent cerebral infarct as the dependent variable in hemodialysis patients

	SCI		
	Odds ratio	95% CI	*P*
Age	1.02	0.94-1.09	NS
Sex	1.15	0.35-3.80	NS
BMI	1.12	0.86-1.44	NS
Dialysis duration	1.13	0.71-1.77	NS
Diabetes mellitus	1.64	0.48-5.56	NS
Hypertension	2.14	0.51-9.03	NS
Hyperlipidemia	1.71	0.52-5.67	NS
Smoking habit	4.80	1.11-20.8	.0361
IHD	5.40	1.01-26.9	.0489
Hematocrit	0.94	0.78-1.13	NS
T-cholesterol	1.00	0.97-1.01	NS
Triglyceride	1.01	0.97-1.03	NS
HDL-C	0.94	0.90-0.99	.0365
Fasting plasma glucose	1.01	0.98-1.03	NS
hemoglobin A_{1c}	1.13	0.67-1.91	NS
Uric acid	1.36	0.99-1.85	NS
Homocysteine	1.22	1.10-1.36	.0003
Ejection fraction	0.98	0.91-1.06	NS
$LVID_d$	1.05	0.89-1.24	NS
$LVID_s$	1.04	0.91-1.20	NS
$IVST_d$	1.42	0.97-2.08	NS
PWT_d	1.56	1.04-2.34	.0330
LVMI	1.02	1.00-1.04	.0460
E/*A* ratio	0.92	0.84-1.05	NS
Deceleration time	1.02	0.99-1.04	NS

Significant predictors of SCI were explored among 6 parameters: sex (female = 0, men = 1), diabetes mellitus (absent = 0, present = 1), hypertension (absent = 0, present = 1), hyperlipidemia (absent = 0, present = 1), smoking habit (absent = 0, present = 1), and IHD (absent = 0, present = 1). See Tables 1 and 2 for other abbreviations.

Table 5
Univariate logistic regression analysis with silent cerebral infarct as the dependent hemodynamic parameter in HD patients

	SCI		
	Odds ratio	95% CI	*P*
24 h			
Systolic ambulatory blood pressure (mm Hg)	1.04	0.97-1.11	NS
Diastolic ambulatory blood pressure (mm Hg)	0.99	0.93-1.05	NS
Heart rate (beats/min)	1.05	0.93-1.18	NS
Daytime			
Systolic ambulatory blood pressure (mm Hg)	1.03	0.97-1.11	NS
Diastolic ambulatory blood pressure (mm Hg)	0.98	0.92-1.04	NS
Heart rate (beats/min)	1.03	0.92-1.14	NS
Nighttime			
Systolic ambulatory blood pressure (mm Hg)	1.10	1.01-1.19	.0276
Diastolic ambulatory blood pressure (mm Hg)	1.04	0.97-1.11	NS
Heart rate (beats/min)	1.17	1.02-1.33	.0262
Nondippers	3.67	1.02-13.1	.0461

The echocardiographic findings are summarized in Table 3. Ejection fraction, left ventricular dimensions at end diastole and end systole, and intraventricular septal wall thickness at end diastole were similar in the 2 groups. However, the posterior wall thickness at end diastole and LVMI were higher in the with-SCI than in the without-SCI group ($P = .0256$ and $P = .0375$, respectively). With regard to the left ventricular diastolic function, the *E*/*A* ratio was lower in the with-SCI group compared with the without-SCI group ($P = .0458$). Deceleration time was similar between the 2 groups.

In univariate logistic regression analysis, the risk of SCI was associated with smoking (odds ratio [OR], 4.80; 95% CI, 1.11-20.8; $P = .0361$), IHD (OR, 5.40; 95% CI, 1.01-26.9; $P = .0489$), HDL-C (OR, 0.94; 95% CI, 0.90-0.99; $P = .0365$), homocysteine (OR, 1.22; 95% CI, 1.10-1.36; $P = .0003$), posterior wall thickness at end diastole (OR, 1.56; 95% CI, 1.04-2.34; $P = .0330$), and LVMI (OR, 1.02; 95% CI, 1.00-1.04, $P = .0460$) as the dependent metabolic and echocardiographic parameters in HD patients (Table 4).

In univariate logistic regression analysis, the risk of SCI was associated with nighttime sABP (OR, 1.10; 95% CI, 1.01-1.19; $P = .0276$), nighttime heart rate (OR, 1.17; 95% CI, 1.02-1.33; $P = .0262$), and nondippers (OR, 3.67; 95% CI, 1.02-13.1; $P = .0461$) as the dependent hemodynamic parameters in HD patients (Table 5).

Multivariate logistic analysis identified plasma tHcy in the HD patients as an independent and significant risk factor for SCI (OR, 1.22; 95% CI, 1.10-1.36; $P = .0003$).

4. Discussion

In the present study, measurement of metabolic parameters revealed that serum HDL-C was lower and tHcy was higher in the with-SCI group than in the without-SCI group. With regard to ABP findings, the nighttime sABP and heart rate were higher in the with-SCI group than in the without-SCI group. Furthermore, multiple logistic analysis revealed that hyperhomocysteinemia was an independent risk factor for the presence of SCI in HD patients.

Silent cerebral infarction is an important risk factor for stroke, and there are several reports concerning SCI in the general population. From the results of MRI studies, Kobayashi et al [6] reported that the incidence of SCI was 10.6% in 993 neurologically healthy adults without a history of cerebrovascular diseases. The Hisayama community-based study showed that the incidence of SCI was 12.9% [21]. The prevalence of SCI in HD patients is thought to be about 5 times greater than in the normal population [4,5]. The prevalence of SCI was similar to the proportion (24/44 [54.5%] HD patients) observed in the present study.

The reference range of tHcy is 3 to 15 μ/L [22], but tHcy levels are 3 to 4 times higher in HD patients than in the healthy populations [23]. In addition, several studies have shown a strong, positive, and dose-dependent association between serum tHcy and risk of stroke, which is independent of other vascular risk factors [9,10]. In HD patients, prospective studies linking homocysteinemia to cardiovascular disease confirm that patients with increased plasma tHcy concentrations are more likely to develop fatal and nonfatal atherosclerotic complications [24,25].

What are the mechanisms by which elevated tHcy levels lead to SCI? Elevated tHcy induces oxidative injury to vascular endothelial cells and impairs the production of nitric oxide, a strong vascular relaxing factor, by the endothelium [26,27]. Hyperhomocysteinemia also enhances platelet adhesion to endothelial cells [28], promotes growth of vascular smooth muscles cells [29], and is associated with higher levels of prothrombotic factors such as β-thromboglobulin, tissue plasminogen activator, and factor VIIc [30]. In addition, Woo et al [31] showed that oral folate supplementation improves the arterial endothelium-dependent vascular function of the brachial artery in healthy subjects with mild hyperhomocysteinemia. In another study, administration of folate and vitamin B_{12} for 9 weeks to patients with coronary heart disease and hyperhomocysteinemia improved vascular endothelial function as assessed by brachial artery flow-mediated dilatation [32]. Based on these results, tHcy appears to be not only a risk factor for arterial sclerosis, but possibly could act as a pathophysiologic modulator causing other endothelial dysfunctions. The strong association observed in our study between homocysteine levels and risk of lacunar infarction should be noted.

Lack of a nocturnal fall in blood pressure (nondipper) is common among HD patients [33]. Liu et al [34] concluded that nondipping is a potent predictor of cardiovascular mortality and is associated with autonomic dysfunction in HD patients. In addition, Kawamura et al [35] reported that left ventricular hypertrophy is associated with cerebrovascular events in Japanese HD patients. In the present study, the percentage of nondippers and the night systolic ABP, night heart rate, and LVMI were all higher in the with-SCI group than in the without-SCI group.

The percentage of smokers was higher in the with-SCI group than in the without-SCI group. Howard et al [36] reported that smoking is related to the prevalence of SCI. Smoking affects the vascular tree via several different interactive mechanisms [37]. Nicotine and carbon monoxide separately produce tachycardia, hypertension, and vasoconstriction and both produce direct endothelial damage. Smoking also affects vaso-occlusive factors such as platelet aggregation, plasma viscosity, and fibrinogen levels [37].

First, univariate logistic regression analysis was performed for each factor in Tables 4 and 5, and the analysis showed that HDL-C, homocysteine, nighttime systolic ABP, nighttime heart rate, nondipper, PWT_d, LVMI, IHD, and smoking are all risk factors for SCI in HD patients. Second, to determine significant risk factors from the above ones, multiple logistic regression analysis was performed. A model selection procedure was used for this objective, and homocysteine was statistically decided to be a significant risk factor of the presence of SCI in HD.

There are several limitations to this study. Firstly, the study included a relatively small number of patients and did not include age-matched control subjects. Secondly, we did not measure nutritional status, that is, serum concentrations of folate and vitamins B_6 and B_{12}, which affect homocysteine metabolism [38]. Thus, it remains uncertain whether nutritional status affected the risk of ischemic stroke in HD patients. Finally, the most frequent genetic defect in homocysteine metabolism involves the enzyme methylenetetrahydrofolate reductase [39]. A common polymorphism (C677T) is associated with hyperhomocysteinemia, the highest levels of homocysteine being found in those with the TT genotype. We did not investigate this genetic factor in the present study. Further clinical investigations are needed to determine the relationship between genetic factors and SCI in HD patients.

In conclusion, our study indicates that chronic renal failure maintained by HD increases the prevalence of SCI and that plasma homocysteine level is significantly associated with SCI in HD patients.

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