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Homocyst(e)ine and Atherosclerosis in Patients on Chronic Hemodialysis

Hyperhomocyst(e)inemia is an established risk factor for atherosclerosis. We performed this study to identify the correlating variables and risk factors for atherosclerosis, as measured by the atherosclerotic score (AS), and to determine the relative risk for cardiovascular disease in relation to plasma homocyst(e)ine levels in patients on chronic hemodialysis. We evaluated and measured 61 patients on chronic hemodialysis for clinical and biochemical parameters including atherosclerotic score (AS) and plasma homocyst(e)ine. We divided patients into high and low groups, first, by the mean AS, and second, by the median value of plasma total homocyst(e)ine levels. Then we compared the variables between the two groups. Out of the 61 patients, the median plasma total homocyst(e)ine level was 24.4 μmol/L (mean±SD, 27.7±17.4; range, 9.8-127.4 μmol/L), and the median AS was 5 (mean±SD, 6.2±2.8; range, 3-13) out of a possible 20 points. AS was significantly correlated with plasma total homocyst(e)ine levels ($r=0.37$) and age ($r=0.67$). Through multivariate analysis, plasma total homocyst(e)ine level and age were determined as significant risk factors for the high-AS group ($p<0.05$). However, plasma total homocyst(e)ine level did not correlate with age ($p>0.05$). Eighteen of the 61 patients, presented with cardiovascular disease until the present study, had an AS>6. Cardiovascular disease was found more often in the high-homocyst(e)ine group (>24.4 μmol/L) than in the low-homocyst(e)ine group (odds ratio, 9.3; 95% confidence interval, 2.3-37.4). Regardless of age, hyperhomocyst(e)inemia (especially homocyst(e)ine levels >24.4 μmol/L) is a risk factor that can be modified for the development of cardiovascular disease in patients on chronic hemodialysis.

Key Words : *Atherosclerosis; Dialysis; Homocysteine*

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INTRODUCTION

Homocyst(e)ine is a sulfur amino acid produced by the metabolism of methionine. The major acquired causes of hyperhomocyst(e)inemia, defined as fasting plasma total homocyst(e)ine levels > 13.9 μmol/L, are chronic renal failure and deficiencies of folate, vitamin B_{12} or vitamin B_6 (1, 2). The major genetic cause of hyperhomocyst(e)inemia, homocyst(e)inuria is a rare autosomal recessive disorder, that is usually due to enzyme cystathionine β-synthase deficiency (3). Because patients homozygous for homocyst(e)inuria develop premature cerebral, peripheral and coronary atherosclerosis and thrombosis, an association between homocyst(e)ine and atherosclerosis has been proposed (4).

Recently, hyperhomocyst(e)inemia has been established as an independent risk factor for atherothrombotic disease (5-9). Moreover, hyperhomocyst(e)inemia has been proposed to be an independent risk factor for atherosclerosis in patients with chronic uremia (10-12). Atherosclerosis can be evaluated by many methods, such as angiographic visualization, Doppler techniques, exercise electrocardiogram, radionuclide imaging, digital phlethysmography, and fundoscopic examination. We used the atherosclerotic score (AS) system (13) for the evaluation of artherosclerosis, because it is less invasive and less expensive than some of the other methods.

The aims of this study were to identify the correlating variables and risk factors for atherosclerosis, as measured by AS, and to determine the relative risk for cardiovascular disease in relation to homocyst(e)ine levels in patients on chronic hemodialysis.

MATERIALS AND METHODS

Materials

We studied 61 patients on chronic hemodialysis (29 men and 32 women, 17 to 78 years of age) at Korea University

Table 1. Atherosclerotic score (AS)

Parameters	Score			
	1	2	3	4
Chest roentgenogram	Calcification of aortic knob	Calcification of aortic arch (<1/4)	Calcification of aortic arch (1/4-1/2)	Calcification of aortic arch (>1/2)
Ocular fundus (Scheie)	S1	S2	S3	S4
EKG	Normal	Horizontal ST depression (<0.1 mV)	Horizontal ST depression (>0.1 mV)	Q wave History of MI
CVD	No	History of TIA	No	History of CI
ASO	No	No	No	(+)

Adapted from ref. 13, by permission of the author. CVD, cardiovascular disease; MI, myocardial infarction; TIA, transient ischemic attack; CI, cerebral infarct; ASO, atherosclerosis obliterans.

Hospital in October, 1996. The mean duration of hemodialysis was 36.3±26.3 months (range, 6 to 124 months). Out of 61 patients, 18 presented with cardiovascular disease, 6 with cerebrovascular disease, 5 with peripheral vascular disease, 8 with coronary heart disease, and one patient presented with both cerebrovascular disease and coronary heart disease until the present. Cerebrovascular disease was confirmed by typical neurologic abnormality or by computerized tomography scan or magnetic resonance imaging of the brain. Peripheral vascular disease (atherosclerotic narrowing of limbs) was confirmed by angiography or Doppler ultrasonography, and coronary heart disease (angina, myocardial infarction) was confirmed by chest pain/changes on EKG or coronary angiography.

Methods

Atherosclerosis was evaluated by means of chest roentgenogram, ocular fundus (14), EKG, and history of vascular disease. Patients were assigned 2-20 points according to the AS system (13) (Table 1). We also obtained informations on sex, age, duration of dialysis, history of hypertension, history of diabetes mellitus, smoking behavior, and use of erythropoietin. We measured BUN, serum creatinine, hematocrit, albumin, folate, vitamin B12, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglyceride, total lipid, and uric acid. To measure plasma total homocyst(e)ine levels, we obtained venous blood samples before dialysis after an overnight fasting and stored the plasma at -70℃ until measured by a high-performance liquid chromatography (HPLC) (HP 1090 II, Hewlett Packard, Waldbronn, Germany, Column: Lichrospher RP-C18) with programmable fluorescence detector (HP 1046A, Hewlett Packard, wavelength 385 nm/515 nm), as previously described (15). The intra-assay and inter-assay coefficients of variation for this assay were below 7.5%.

To analyze the data, we first examined the correlation between AS and the variables listed above, including homocyst(e)ine level. Second, to identify risk factors for atherosclerosis, we divided patients into two groups according to their high or low AS (by the mean of AS) and compared the variables between the two groups. Finally, to determine the relative risk of cardiovascular disease, we again divided the patients into two groups according to their high or low level of plasma total homocyst(e)ine (by the median value of plasma total homocyst(e)ine) and once again compared the variables between the two groups.

Statistical analysis

Results were expressed as mean±S.D. Statistical analysis was done by Mann-Whitney U test, Student *t*-test, x^2 test, Spearman's correlation, and logistic regression analysis. A *p*-value < 0.05 was considered significant.

RESULTS

The distribution of AS in patients on chronic hemodialysis is shown in Fig. 1. The median AS was 5 points (mean,

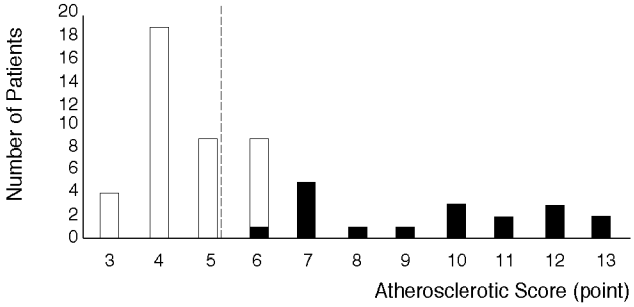

Fig. 1. Distribution of atherosclerotic score in 61 patients on chronic hemodialysis. The median value of atherosclerotic score was 5, and the mean value of aterosclerotic score was 6.2. Open bars express patients without vascular disease, and closed bars express patients with vascular disease.

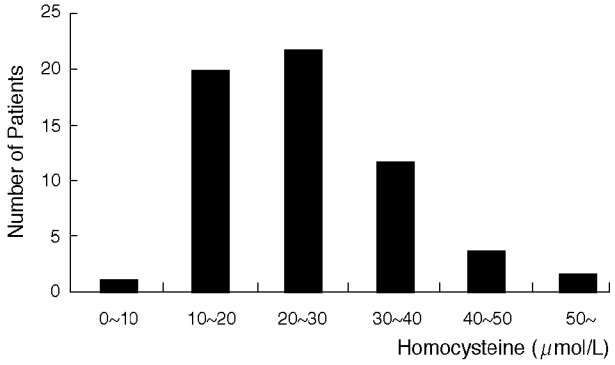

Fig. 2. Distribution of plasma total homocyst(e)ine levels in 61 patients on chronic hemodialysis. The median value of homocyst(e)ine was 24.4 μmol/L.

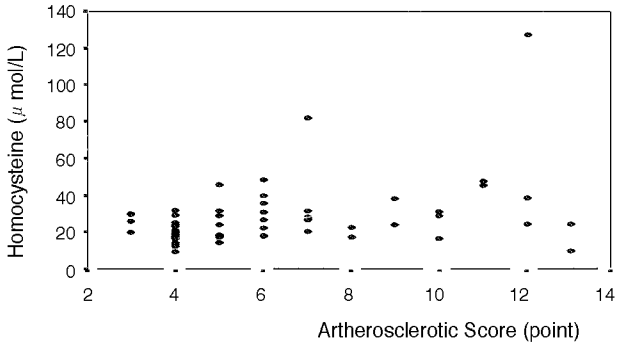

Fig. 3. Correlation between plasma total homocyst(e)ine levels and atherosclerotic score in 61 patients on chronic hemodialysis (r=0.372, p=0.003).

6.2±2.8; range, 3-13). The 18 patients, presented with vascular disease, had > 6 points.

The distribution of plasma total homocyst(e)ine levels is shown in Fig. 2. The median level was 24.4 μmol/L (mean, 27.7±17.4; range, 9.8-127.4 μmol/L). The normal range for plasma total homocyst(e)ine level in 50 healthy subjects 19 to 55 years of age was 5.1 to 13.9 μmol/L, as determined in the same laboratory. According to this normal range, total plasma homocyst(e)ine levels were elevated in 57 of the 61 patients.

AS correlated significantly with plasma total homocyst(e)ine levels (*r=0.37; p=0.003*) (Fig. 3) and with age (*r=0.67; p=0.001*). Furthermore, AS was higher in patients with diabetes (8.7±2.9) than in patients without diabetes (5.8±2.5) (*p=0.003*). However, no significant correlation with AS was observed for the following variables: BUN, serum creatinine, hematocrit, albumin, folate, vitamin B_{12}, total-cholesterol, HDL-cholesterol, LDL-cholesterol, triglyceride, total lipid, uric acid, duration of dialysis. No significant differences of AS were in sex, hypertension, smoking behavior, and use of erythropoietin.

Table 2. Biochemical variables in low- and high-AS groups

Variables	low AS (n=32)	high AS (n=29)
Hcy (μmol/L)	21.8±7.4	34.2±22.5*
BUN (mg/dL)	86.3±19.4	79.5±20.0
Creatinine (mg/dL)	14.7±3.4	12.1±3.9**
Hematocrit (%)	26.5±3.2	26.5±4.2
Albumin (g/dL)	4.3±0.4	4.3±0.3
Folate (ng/mL)	9.3±5.2	9.7±6.5
Vitamin B_{12} (pg/mL)	748.7±180.7	860.2±359.8
Total-C (mg/dL)	148.2±35.3	147.9±32.6
HDL-C (mg/dL)	33.3±12.0	33.8±10.0
LDL-C (mg/dL)	76.5±36.5	84.4±24.2
Triglyceride (mg/dL)	182.8±109.5	135.3±69.5†
Total lipid (mg/dL)	713.4±145.5	656.1±146.0
Uric acid (mg/dL)	8.3±1.8	7.6±1.7

AS: atherosclerotic score, Low AS: 3-5 points; high AS: 6-13 points. Hcy, homocyst(e)ine; Total-C, total cholesterol; HDL-C, HDL-cholesterol; LDL-C, LDL-cholesterol. Results are expressed as the mean± S.D. Values that are significantly different from those in the low-AS group are indicated by: * *p<0.01*, † *p<0.05*

Table 3. Clinical variables of the low- and high-AS groups

Variables	low AS (n=32)	high AS (n=29)
Age (years)	41.8±11.5	57.1±11.1*
Sex (M/F)	16/16	13/16
Dialysis duration (months)	35.3±21.8	37.5±30.8
Hypertension	22	17
Smoking	7	5
Use of erythropoietin	26	8
Diabetes mellitus**	1	8†

Low AS: 3-5 points; high AS: 6-13 points. Results are expressed as the mean±S.D. and number of patients. Values that are significantly different from those in the low-AS group are indicated by: * *p<0.01*, † *p<0.05*

To identify the risk factors for atherosclerosis, we compared variables in patients divided into two groups by the mean AS: high (6-13 points) and low (3-5 points). By univariate analysis, plasma total homocyst(e)ine level was significantly higher in the high-AS group (29 patients) than in the low-AS group (32 patients) (Table 2). Age, history of diabetes, serum creatinine, and triglyceride levels were also significant variables in the high-AS group (Table 2, 3). By multivariate analysis, only plasma total homocyst(e)ine level and age were significant risk factors in the high-AS group (age: *R=0.272, p=0.001, Exp (B)=1.113;* homocyst(e)ine: *R=0.152, p=0.023, Exp (B)=1.119*). However, plasma total homocyst(e)ine level was not correlated with age (*r=0.247, p=0.06*).

To determine the differences of clinical and biochemical parameters according to serum total homocyst(e)ine level, we again divided the patients into two groups, those above

Table 4. Clinical variables of the low- and high-Hcy groups

Variables	low Hcy (n=31)	high Hcy (n=30)
Age (years)	45.9±13.1	52.3±13.6
Sex (M/F)	11/20	18/12
Dialysis duration (months)	35.0±23.7	37.7±29.0
Hypertension	22	17
Smoking	6	6
Use of erythropoietin	24	21
Diabetes mellitus	3	6
Vascular disease	3	15*

Low-Hcy, < 24.4 μmol/L; high Hcy, > 24.4 μmol/L. Results are expressed as the mean±S.D. and number of patients. Values that are significantly different from those in the low-Hcy group are indicated by : * *p<0.01*

Table 5. Biochemical variables in the low- and high-Hcy groups

Variables	low Hcy (n=31)	high Hcy (n=30)
BUN (mg/dL)	84.0±19.6	82.0±20.4
Creatinine (mg/dL)	12.5±3.1	13.8±4.3
Hematocrit (%)	26.7±3.5	26.3±3.8
Albumin (g/dL)	4.2±0.4	4.3±0.4
Folate (ng/mL)	8.4±4.6	10.6±6.7
Vitamin B_{12} (pg/mL)	784.0±250.1	820.0±317.8
Total-C (mg/dL)	147.2±31.3	149.0±36.6
HDL-C (mg/dL)	33.5±11.7	33.5±10.5
LDL-C (mg/dL)	78.0±34.4	82.5±28.1
Triglyceride (mg/dL)	161.4±101.1	159.0±89.9
Total lipid (mg/dL)	702.2±128.1	669.5±165.5
Uric acid (mg/dL)	8.1±2.0	7.9±1.4

Low-Hcy, < 24.4 μmol/L; high Hcy, > 24.4 μmol/L. Abbreviations are seen as in other tables. Results are expressed as the mean±S.D. and number of patients.

and those below the median value of plasma total homocyst(e)ine (24.4 μmol/L). Cardiovascular disease was more prevalent in the high-homocyst(e)ine group than in the low-homocyst(e)ine group (odds ratio, 9.3; 95% confidence interval, 2.3-37.4). However, other clinical and biochemical variables were not different between the two groups (Table 4, 5).

DISCUSSION

We showed that plasma total homocyst(e)ine levels and age were the significant correlating variables and risk factors for the atherosclerosis (measured by AS) in patients on chronic hemodialysis. Furthermore, the higher values of plasma total homocyst(e)ine (>24.4 μmol/L) were associated more frequently with cardiovascular disease.

The advantage of using AS to measure atherosclerosis was that the invasive and expensive diagnostic examinations for atherosclerosis was not necessary. For AS, only simple tests such as EKG, chest roentgenogram, fundus evaluation, and history of cardiovascular disease were needed (Table 1). The patients presented with cardiovascular disease had an AS >6. (Fig. 1). However, in our study, the traditional risk factors for atherosclerosis did not significantly correlate with AS (Table 2, 3). It is well known that the atherosclerosis of patients on chronic dialysis is not explained simply by traditional risk factors, as it is in the general population (10).

In the original Framingham Study cohort, Selhub et al. (16) found age-related increases in plasma total homocyst(e)ine levels. However, our data showed no significant correlation between age and plasma total homocyst(e)ine levels. Similarly, Kim et al. (13) reported that plasma total homocyst(e)ine levels did not correlate with the mean age in patients on chronic dialysis. Therefore, regardless of age, plasma total homocyst(e)ine levels may be an independent risk factor for atherosclerois in these patients.

By univariate analysis, history of diabetes, serum creatinine and triglyceride levels were also determined as significant variables for atherosclerosis (Table 2, 3). It is known that homocyst(e)ine levels may be correlated positively with plasma creatinine. (*r* values from 0.49 to 0.62) (12, 17). In contrast, we found that serum creatinine in the high-AS group was lower than that in the low-AS group. The reason for this finding may be the significant difference in age between the two groups (Table 3). Because serum creatinine levels were decreased in the elderly patients, and a history of diabetes was prevalent in the elderly of our patients, both variables became insignificant by multivariate analysis. Also, when serum triglyceride values >400 mg/dL were excluded (3 patients in the low-AS group, 1 patient in the high-AS group), serum triglyceride became insignificant even by univariate analysis.

Several studies have shown a significant relationship between increased plasma homocyst(e)ine levels and vascular disease at various sites. The association of homocyst(e)ine with coronary arterial diseases has been pronounced in case-control (5, 6), cross-sectional, and prospective studies (18).

Hyperhomocyst(e)inemia has also been observed frequently in patients with cerebrovascular disease (5, 8, 9). Furthermore, many studies have shown an association of high plasma homocyst(e)ine levels with peripheral arterial diseases (5, 7, 19).

The mechanisms by which homocyst(e)ine induces atherosclerosis and thrombosis are not clear. However, experimental evidence has confirmed the atherogenic effects of hyperhomocyst(e)inemia. Harker et al. (20) found that infusion of homocyst(e)ine led to patch endothelial desquamation comprising about 10% of the aortic surface. Wall et al. (21) suggested that an excess amount of homocyst(e)ine induced endothelial damage and detachment in endothelial

cell culture. Tsai et al. (22) found that homocyst(e)ine had a growth-promoting effect on vascular smooth cells and a growth-inhibiting effect on endothelial cells. Other studies showed that hyperhomocyst(e)inemia induced oxidation of low-density lipoprotein (23) and increased incorporation of lipoprotein(a) into fibrin (24). Therefore, endothelial injury may be a possible explanation of homocyst(e)ine-induced atherosclerosis.

Homocyst(e)ine has been associated with free oxygen radicals (21, 25), depressed prostacyclin production (26), increased factor V activity (27), reduced protein C activity (28), and inhibited von Willebrand factor in cultured endothelial cells (29). Thus, these coagulation abnormalities may contribute to thrombogenic activity in hyperhomocyst(e)inemia.

Lindner et al. (30) reported accelerated atherosclerosis in prolonged maintenance hemodialysis, the validity of their study was supported by several subsequent reports (31). Risk factors for atherogenesis in chronically uremic patients are physical factors such as hypertension, and metabolic factors such as dyslipidemia, glucose intolerance, hyperhomocyst(e)inemia, smoking, secondary hyperparathyroidism, and vitamin E deficiency (31).

Our data showed that plasma total homocyst(e)ine levels were elevated above the normal range in 93% of patients on chronic hemodialysis. Wicken et al. (32) demonstrated that homocyst(e)ine-cysteine mixed disulfide was twofold higher in hemodialysis patients than in control subjects and decreased about 50% after hemodialysis. Kim et al. (13) showed a high prevalence of hyperhomocyst(e)inemia in both hemodialysis and continuous ambulatory peritoneal dialysis patients, and showed that plasma total homocyst(e)ine levels did not correlate with age, plasma vitamin B_6 levels, protein catabolic rate, KT/V (urea kinetic model), or residual renal function. On the other hand, Chauveau et al. (12) observed increased plasma total homocyst(e)ine levels from an early stage of chronic renal failure and saw further progression of hyperhomocyst(e)inemia as renal function worsened.

The mechanism of hyperhomocyst(e)inemia in chronic renal failure is not clearly understood. Decreased renal excretion of homocyst(e)ine is not the principal cause of hyperhomocyst(e)inemia, because only small amounts (<20%) are excreted in urine (12), and fractional clearance of homocyst(e)ine increases with decline in renal function (33). Impaired hepatic metabolism related to the uremic environment may led to decreased catabolism of homocyst(e)ine (33). In addition, the presence of hyperhomocyst(e)inemia with normal or increased folate, vitamin B_{12}, and B_6 levels suggests an impaired vitamin-dependent metabolic process (2).

Because atherosclerosis is a major cause of morbidity and mortality in patients with chronic uremia, the modification of risk factors for atherosclerosis may improve the prognosis. Our data showed that plasma homocyst(e)ine and age were significant risk factors for atherosclerosis. Age can not be modified, but lowering homocyst(e)ine could be attempted. Some studies have shown that folic acid supplementation reduced homocyst(e)ine levels despite normal or increased plasma folate levels (1, 2). Wilcken et al. (34) observed that elevated plasma homocyst(e)ine levels were reduced by administration of 5 mg folic acid daily for 15 days. Alternatively, vitamin B_{12} treatment alone has been less reliably effective in lowering homocyst(e)ine levels, and vitamin B_6 therapy is probably effective only in the deficiency state or in combination with folate administration (1, 2, 35).

However, it is not known which level of plasma homocyst(e)ine could be reached by lowering homocyst(e)ine in patients on chronic hemodialysis. In the present study, cardiovascular disease was more prevalent in the group with a higher level of plasma total homocyst(e)ine (>24.4 μmol/L). To date, there is no "gold-standard" for measuring plasma homocyst(e)ine. Because of the various methods of measurement including ion-exchange chromatography, gas chromatography-mass spectrometry, radioenzymatic assay, and high-performance liquid chromatography, there is no universally accepted range of normal values (35). Until a standard method of measuring homocyst(e)ine is settled, we suggest that, for the prevention of atherosclerosis, hyperhomocyst(e)inemia should be controlled by lowering plasma total homocyst(e)ine <24.4 μmol/L, when normal levels range from 5.1 to 13.9 μmol/L by HPLC with fluorescence detector. In conclusion, our results suggest that hyperhomocyst(e)inemia (>24.4 μmol/L) may be a risk factor that can be modified for the development of atherosclerosis in patients on chronic hemodialysis.

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