The Association Between Hyperhomocysteinemia and Coronary Artery Disease in Non-Diabetic End-Stage Renal Disease Patients on Regular Hemodialysis

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ABSTRACT

Coronary artery disease (CAD) is an important cause of death in end-stage renal disease (ESRD) patients on regular hemodialysis. The high risk of CAD occurrence in ESRD patients is partially due to a high prevalence of established atherosclerotic risk factors, which are hypertension, diabetes and dyslipidemia. However, unique renal-related risk factors are also likely to contribute to this high risk of CAD. The high prevalence of hyperhomocysteinemia in ESRD patients is of interest because of the probable cardiovascular risk associated with the increase of total plasma homocysteine concentration. The aim of this study was to evaluate the role of homocysteine as a risk factor for CAD in non-diabetic ESRD patients on regular hemodialysis.

Total fasting plasma homocysteine, total cholesterol, LDL cholesterol, HDL cholesterol, triglyceride, hypertension and smoking habit were documented from 80 non-diabetic ESRD patients on regular hemodialysis (48 men, 32 women; mean age 54.5±6.5 years). Twenty-two (27.5%) among these patients suffered from CAD according to ECG and echocardiographic criteria. The risk of CAD was analyzed using a stepwise multiple logistic regression. Total fasting plasma homocysteine concentration and other risk factors for CAD were also determined in 80 age- and sex-matched normal controls.

Total fasting plasma homocysteine concentration was significantly higher in non-diabetic ESRD patients than in normal controls (26.0±1.5 versus 14.6±1.3 μmol/L; $p<0.01$). Hyperhomocysteinemia was observed in 92.5% ESRD patients. Homocysteine concentration was significantly higher in ESRD patients with CAD than without CAD (33.8±1.4 versus 23.5±1.5 μmol/L; $p<0.01$). High total plasma homocysteine concentration and hypertension were independently associated with CAD in non-diabetic ESRD patients on regular hemodialeine concentration in the upper tertile (≥30.6 μmol/L) had an adjusted odds ratio of 2.95 (CI, 1.02 to 8.53; $p<0.05$). In ESRD patients, the intake of folic acid is the only factor associated with total plasma homocysteine concentration. The increase of total plasma homocysteine concentration in normal controls was associated with increased age and smoking habit.

This study concludes that a high total plasma homocysteine concentration is an independent risk factor for coronary artery disease in non-diabetic ESRD patients on regular hemodialysis.

Keywords:Non-diabetic ESRD patients, hyperhomocysteinemia, CAD

INTRODUCTION

In 2000, there were approximately 3,000 patients with end-stage renal disease (ESRD) on regular hemodialysis treatment in Indonesia, or approximately 15 patients per million inhabitants.[1] Although there is no data on the prevalence of ESRD in Indonesia, only 20% - 30% patients with ESRD who are hospitalized have a chance to receive regular hemodialysis treatment.[2]

Compared to the general population, the life expectancy of ESRD patients on regular hemodialysis is dramatically reduced.[3] Death are due mainly to cardiovas-

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cular diseases (CVD), accounting for about 50% of all causes.[3] The risk of CVD is far greater for patients with ESRD. Even after stratification by age, gender and race, the CVD mortality in dialysis patients is 10 to 20 times higher than in the general population. Improved survival will partially depend upon the identification and reduction of risk factors, and more effective treatment of coronary artery disease (CAD).[4]

The high risk of CAD in ESRD patients is partially due to a high prevalence of established atherosclerotic risk factors, which are hypertension, diabetes and dyslipidemia. However, unique renal-related risk factors are also likely to contribute to this high risk of CAD.[4]

Prominent among these unique renal-related risk factors are elevated levels of sulfur-containing amino acid homocysteine.[5] Homozygous genetic disorders result in marked hyperhomocysteinemia and are clearly associated with premature and extensive thrombosis and atherosclerosis.[6] In contrast, results of studies among the general population indicated less or no predictive ability for plasma homocysteine in cardiovascular disease.[7]

Homocysteine concentration rises in ESRD. Homocysteine values are roughly threefold that of the general population,[8] and usually have concentrations in range of 20-80 µmol/L.[9] The high prevalence of hyperhomocysteinemia in ESRD patients is of interest because of the probable cardiovascular risk associated with the increase of total plasma homocysteine concentration. It was the aim of this study to evaluate the role of homocysteine as a risk factor for CAD in non-diabetic ESRD patients on regular hemodialysis.

METHODS

Subjects

This study was conducted between August 1999 to June 2000 at the renal unit of Hasan Sadikin General Hospital and Ny. RA. Habibie Hemodialysis Center, Bandung.

Eighty patients with established end-stage renal disease were studied (48 men and 32 women; mean age 54.5±6.5 years). All patients were on hemodialysis. The etiology of renal failure was due to the following: chronic pyelonephritis (n=28), chronic glomerulonephritis (n=20), obstructive uropathy (n=13), urate nephropathy (n=6), hypertensive renal disease (n=2), polycystic kidney disease (n=1), and unknown (n=10).

The inclusion criteria were age ≥ 45 years and receiving twice weekly 4-hour sessions of hemodialysis for ≥ 3 months. The exclusion criteria were diabetes, history of arteriovenous fistula thrombosis, deep vein thrombosis or peripheral vascular disease, history of TIA or stroke, and receiving lipid lowering agents, anticonvulsants, or theophylin.

To examine the association between homocysteine and CAD, consecutive patients with ESRD were divided into two groups based on presence of CAD by ECG and echocardiographic criteria.

To determine the factors associated with homocysteine concentration, consecutive healthy subjects attending the out-patients health screening program at Hasan Sadikin General Hospital served as normal controls, who were matched by age (± 2.5 years) and sex to ESRD patients. Subjects with clinical or ECG evidence of CAD, clinical history of renal disease or abnormal serum blood urea nitrogen (BUN) or creatinine levels, or those using lipid lowering agents, folic acid, B_6, B_{12}, or multivitamins in the past six months were excluded.

Clinical and Laboratory Data Acquisition

History of smoking, hypertension, diabetes, history of arteriovenous fistula thrombosis, deep vein thrombosis, peripheral vascular disease, TIA or stroke was obtained by interview, physical examination, and medical record review.

All ESRD patient and control bloods were drawn after an overnight fast (12 hours). ESRD patients were phlebotomized immediately prior to their next dialysis treatment, which was between 70 and 90 hours since the end of their previous dialysis. Total cholesterol, LDL cholesterol, HDL cholesterol, and triglyceride were determined using automated enzymatic methods. Plasma glucose, serum creatinine, and blood urea nitrogen (BUN) were assessed by standard clinical chemistry laboratory methods. Total homocysteine was determined in EDTA plasma by flouresence polarization immunoassay (FPIA)[10] (IMx Analyzer; Abbott, Chicago, Illinois). Within 1 hour of collection blood samples were centrifuged, and then the EDTA plasma was separated and stored at -20°C until analysis.

Operational Definitions

End-stage renal disease was defined as a requirement for maintenance dialysis. All were on a schedule for twice weekly 4-hour sessions of hemodialysis.

Coronary artery disease was diagnosed by ECG criteria supported with an abnormal wall motion in segmental analysis (hypokinetic, akinetic, or dyskinetic) documented at the time of echocardiography carried out in standard manner.

Subjects were categorized as either non-smokers or smokers (if they were current smokers or if they had quit less than 2 years prior to being interviewed). Smokers were classified as mild smokers (< 10 cigarettes per day), moderate smokers (10-19 cigarettes per day), or heavy smokers (20 cigarettes per day).[3]

Hypertension was considered present based on current use of antihypertensive medication, a systolic blood pressure > 140 mmHg, or a diastolic blood pressure > 90 mmHg on two measurements in different day in the hospital.

Diabetes mellitus was diagnosed by medical record review, or if patients were currently using insulin preparations, oral hypoglycemic agents, or if their fasting glucose concentration was ≥ 126 mg/dl.

Using established guidelines,[11] high total cholesterol, high LDL cholesterol, low HDL cholesterol, and high tryglyceride levels were defined as ≥ 200 mg/dl, > 100 mg/dl, < 35 mg/dl, ≥ 200 mg/dl, respectively.

Total plasma homocysteine concentration was classified as normal (5to15 µmol/L), moderate hyperhomocysteinemia (15 to 30 µmol/L), intermediate hyperhomocysteinemia (30 to 100 µmol/L), and severe hyperhomocysteinemia (>100 µmol/L).[12]

Folic acid intake was assessed with a questionnaire. Folic acid intake was categorized as regularly taken (if they were using a minimum og 1 mg folic acid three times daily in the past six months), not regularly taken (if they did not regularly take folic acid in the past six months), and never taken (if they never took folic acid in the past six months).

Statistical Analysis

Descriptive statistics are reported as frequency and percentage for categorical variables and as mean and standard deviation for continuous variables. The data for total homocysteine, total cholesterol, LDL cholesterol, HDL cholesterol, and triglyceride were transformed to natural logarithms for analysis. The logarithmic transformation reduced the pronounced positive skew and decreased the variation, making the data more nearly normally distributed. The geometric mean are reported for these variables.

Percentages were compared using Pearson's chi squared test or Fisher's exact test, depending on the frequencies. Continuous variables were compared using Student's t-test or ANOVA. Correlations between plasma total homocysteine and other predictor variables were evaluated by Pearson correlations or by Spearman's rho. Multiple linier regression model was used to determine the significant independent association with plasma total homocysteine concentration.

Stepwise multiple logistic regression analysis was performed within the ESRD group to assess the significant independent association between plasma levels of total homocysteine and other cardiovascular risk factors with prevalent of CAD.

Reported p-values are based on two-tailed calculations, and $p < 0.05$ was required for the asumption of statistical significance. All statistical analyses were performed using SPSS 10.0 (SPSS, Inc., Chicago, Illinois).

RESULTS

As illustrated in table 1, patients and normal controls were successfully matched for age and sex. Lower total, LDL, and HDL cholesterol levels were observed among ESRD patients ($p<0.01$). Conversely, total homocysteine levels was markedly increased in ESRD patients than in normal controls (26.0±1.5 vs 14.6±1.3 µmol/L; p=0.000). Levels were not significantly different between men and women both on ESRD patients (26.2±1.5 vs 25.6±1.5 µmol/L; p=0.801) and normal controls (14.9±1.3 vs 14.2±1.4 µmol/L; p=0.461).

Table 1.Comparisons Between ESRD Patients and Normal Controls In Demographic Characteristics and Cardiovascular Risk Factor Profile

Variable	ESRD patients (n = 80)	Normal controls (n = 80)	p
Age (years) *	54.5±6.5	54.0±7	
Male / female *	48/32	48/32	
Smoking	14 (17.5%)	36 (45%)	0.000
Hypertension	56 (70%)	28 (35%)	0.000
Total cholesterol (mg/dl)	161.5±1.3	187.9±1.2	0.000
≥ 200 mg/dl	14 (17.5%)	30 (37.5%)	0.005
LDL cholesterol (mg/dl)	98.8±1.4	112.7±1.3	0.005
≥ 130 mg/dl	14 (17.5%)	23 (28.5%)	0.092
HDL cholesterol (mg/dl)	32.3±1.4	45.0±1.3	0.000
< 35 mg/dl	47 (58.8%)	14 (17.5%)	0.000
Triglyceride (mg/dl)	130.8±1.5	127.6±1.6	0.705
≥ 200 mg/dl	12 (15%)	14 (17.5%)	0.668
Total homocysteine (µmol/L)	26.0±1.5	14.6±1.3	0.000

Values are stated in mean ± SD.
* matched variable.

In univariate analysis, determinants of total homocysteine in normal controls included age, cigarettes smoking, and hypertension. In multivariate analysis, the independent determinants of total homocysteine were age and smoking habit (Table 2). Total homocysteine concentrations tend to be higher with increasing age. Relatively strong correlations were observed in women. However, this correlation did not reach significance in men (Figure 1). Total homocysteine concentration in smokers was significantly different than non-smokers (15.9±1.3 vs 13.7±1.3 µmol/L; p=0.019). Differences in total homocysteine among non-smokers, mild, moderate, and heavy smokers were significant only in men (13.0±1.3; 15.1±1.3; 17.2±1.3; 17.9±1.3 µmol/L respectively; p=0.046).

In univariate analysis, determinants of total homocysteine in ESRD patients included duration of hemodialysis (r=0.295; p=0.009), folic acid intake (r=-0.380; p=0.001), and triglyceride levels (r=0.281; p=0.012). In multivariate analysis, determinants of total homocysteine were duration of hemodialysis and folic acid intake (table 3). However, there was a significant correlation between the duration of hemodialysis and folic acid intake (r=-0.242; p=0.046). With corrected folic acid intake, the correlation between duration of hemodialysis and total homocysteine levels was no longer significant (r=0.206; p=0.068). In this study, independent determinants of total homocysteine in ESRD patients included only folic acid intake. Patients who regularly took folic acid 1 mg three times daily, have significantly different total homocysteine concentrations compared to those who did not regularly or never took folic acid in the past six months (20.6±1.4 vs 28.7±1.4 and 30.6±1.7 µmol/L; p=0.001).

Table 2.Multiple Regression Analysis of Factors Affecting Serum Total Homocysteine Levels In Normal Controls

Variable	Standard regression coefficients (β)	p
Age (years)	0.328	0.004
Male / female	-0.048	0.724
Hypertension	0.161	0.181
Smoking	0.298	0.017
Ln (total cholesterol)	0.041	0.919
Ln (LDL cholesterol)	-0.084	0.816
Ln (HDL cholesterol)	0.159	0.332
Ln (triglyceride)	0.030	0.880
r^2	0.277	0.002

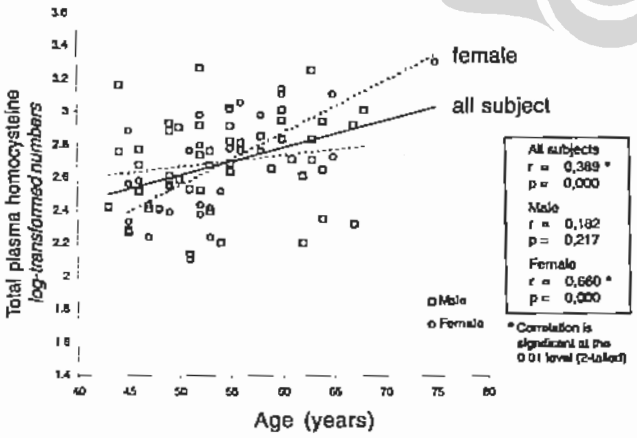

Figure 1. Correlation Beetween Total Homocystein Concentrations and Age in Normal Control

Twenty-two (27.5%) ESRD patients suffered from CAD according to the ECG and echocardiographic criteria. As ilustrated in table 4, a significant difference between subjects with CAD and without CAD was observed only for percentage subjects with hypertension (90.9% vs 62.0%; p=0.012) and mean values of total homocysteine concentration of 33.8±1.4 (vs 23.5±1.5; p=0.000).

Ninety-two point five percent of patients were hyperhomocysteinemic, with values >15 mmol/L. Moderate hyperhomocysteinemia was observed in 44 (55%) patients, and intermediate hyperhomocysteinemia was observed in 30 (37.5%) patients. Since total homocysteine concentrations were frequently elevated in ESRD patients, we divided the ESRD group into tertiles based on total homocysteine concentrations. Compared with the lower two tertiles, patients in the upper tertile of homocysteine values (≥ 30.6 µmol/L) were significantly different only for the duration of hemodialysis (p=0.016) and percentage of subjects with CAD (p=0.015) (table 5). In this study, the cut-off value of total homocysteine concentration as risk factor for CAD was 30.6 µmol/L.

Table 6 shows the results of stepwise multiple logistic regression analysis to determine the independent contribution of each factor to the risk of CAD in ESRD patients. The variables cigarette smoking, total cholesterol ≥ 200 mg/dl, and triglyceride ≥ 200 mg/dl would not be analyzed with the logistic regression models due to low cell counts. In this model, only hypertension and total homocysteine concentrations of ≥ 30.6 µmol/L showed an independent association with CAD in ESRD patients. Other risk factors of age, male sex, high LDL cholesterol, and low HDL cholesterol, were not statistically significant alone or in interaction. Patients with a homocysteine concentrations in the upper tertile (≥30.6

Table 3.Multiple Regression Analysis of Factors Affecting Total Serum Homocysteine Levels in ESRD Patients

Variable	Standard regression coefficients (β)	p
Age (years)	0.004	0.971
Male / female	0.254	0.061
Duration of hemodialysis (mo)	0.260	0.027
Folic acid intake	0.249	0.028
Hypertension	0.182	0.099
Smoking	0.031	0.794
Ln (total cholesterol)	0.058	0.922
Ln (LDL cholesterol)	–0.070	0.890
Ln (HDL cholesterol)	0.124	0.569
Ln (triglyceride)	0.331	0.139
r^2	0.276	0.009

Abbreviations is : Ln = natural logarithm

Table 4.Comparisons between ESRD patients with CAD and without CAD in demographic characteristics and cardiovascular risk factor profile

Variable	ESRD patients		P
	With CAD (n= 22)	Without CAD (n = 58)	
Age (years)	56±6	54±6.5	0.182
Male sex	15 (68.2%)	33 (56.8%)	0.358
Duration of hemodialysis (mo)	43±29	44±37	0.735
Smoking	5 (22.7%)	9 (15.5%)	0.514
Hypertension	20 (90.9%)	36 (62.0%)	0.012
Total cholesterol (mg/dl)	163.5±1.2	160.8±1.3	0.760
≥ 200 mg/dl	3 (13.6%)	11 (18.9%)	0.747
LDL cholesterol (mg/dl)	97.8±1.3	99.1±1.4	0.863
> 100 mg/dl	12 (54.5%)	30 (51.7%)	0.821
HDL cholesterol (mg/dl)	34.3±1.4	31.6±1.4	0.355
< 35 mg/dl	12 (54.5%)	35 (60.3%)	0.638
Triglyceride (mg/dl)	133.6±1.4	129.9±1.5	0.757
≥ 200 mg/dl	3 (13.6%)	9 (15.5%)	1.000
Dyslipidemia	18 (82%)	49 (84%)	0.506
Total homocysteine (µmol/L)	33.8±1.4	23.5±1.5	0.000

ESRD indicates end-stage renal disease
CAD indicates coronary artery disease
Values are mean ± SD.

Table 5.Demographic Characteristics and Cardiovascular Risk Factor Profile of ESRD Patients in Each Tertile of Total Homocysteine Concentration

Variable	Tertile 1 (n=26)	Tertile 2 (n=27)	Tertile 3 (n=27)	p *
Total homocysteine (µmol/L)	16.7±1.2	25.9±1.1	40.0±1.2	
Median	17.6	26.3	39	
Complete range	10.2 – 21.0	21.7 – 30.5	30.6 – 60.7	
Age (years)	55±7	54.5±7	53.5±6	0.343
Male sex	16 (61.5%)	14 (51.8%)	18 (66.7%)	0.385
Duration of hemodialysis (mo)	41±41	34±24	57±35	0.018
Smoking	5 (19.2%)	4 (14.8%)	5 (18.5%)	1.000
Hypertension	19 (73.1%)	15 (55.6%)	22 (81.5%)	0.110
Total cholesterol (mg/dl)	158.8±1.3	160.1±1.2	165.5±1.3	0.521
≥ 200 mg/dl	5 (19.2%)	5 (18.5%)	4 (14.8%)	0.763
LDL cholesterol (mg/dl)	99.3±1.5	96.1±1.3	101.1±1.4	0.657
> 100 mg/dl	13 (50%)	11 (40.1%)	18 (66.7%)	0.070
HDL cholesterol (mg/dl)	34.6±1.4	31.6±1.3	30.9±1.5	0.441
< 35 mg/dl	12 (46.1%)	16 (59.3%)	19 (70.4%)	0.132
Triglyceride (mg/dl)	107.0±1.4	141.6±1.4	147.0±1.4	0.053
≥ 200 mg/dl	1 (3.8%)	6 (22.2%)	5 (18.5%)	0.527
Suffered from CAD	2 (7.7%)	8 (29.6%)	12 (44.4%)	0.015

Values are stated as mean ± SD.
* p value for upper tertile (total homocysteine concentration ≥ 30.6 µmol/L) versus lower 2.

Table 6. Stepwise Multiple Logistic Regression Analysis Revealing Independent Risk Factors for Coronary Artery Disease in ESRD Patients. Backward stepwise (conditional)

	Variable	β	SE	P
Step 1	Hypertension	1.717	0.809	0.034
	Total homocysteine ≥ 30.6 µmol/L	0.972	0.555	0.080
	Age > 50 years by LDL > 100 mg/dl	0.708	0.565	0.210
	HDL < 35 mg/dl by male sex	0.365	0.556	0.512
	Constant	- 3.135	0.865	0.000
Step 2	Hypertension	1.700	0.808	0.035
	Total homocysteine ≥ 30.6 µmol/L	1.029	0.548	0.061
	Age > 50 years by LDL > 100 mg/dl	0.673	0.559	0.229
	Constant	- 2.969	0.820	0.000
Step 3	Hypertension	1.664	0.802	0.038
	Total homocysteine ≥ 30.6 µmol/L	1.082	0.542	0.046
	Constant	- 2.713	0.775	0.000

µmol/L) had an adjusted odds ratio of 2.95 (CI, 1.02 to 8.53; p<0.05). An adjusted odds ratio of 5.3 (CI, 1.1 – 25.4; p<0.05) for CAD was seen for patients with hypertension.

DISCUSSION

This study shows that high total plasma homocysteine concentrations are associated with an increased risk of CAD independent of traditional risk factors in non-diabetic end-stage renal disease patients on regular hemodialysis. This study confirms the results of previous retrospective and prospective studies.[13-17] The pooled relative risk estimate for incident or recurrent cardiovascular diseases conferred by mild to moderate hyperhomocysteinemia in three prospective studies in ESRD patients was 2.8 (95% confidence interval, 1.6 to 5.0).[5]

The ultimate mechanism of hyperhomocysteinemia in renal failure is not completely understood.[5] Decreased urinary homocysteine excretion is an unlikely explanation in view of the small amount of homocysteine that is normally found in urine.[18] Despite *in vitro* studies demonstrating renal tubular metabolism of homocysteine, and rat model evidence of significant *in vivo* renal homocysteine metabolism, nonsignificant mean human renal arteriovenous differences for fasting total homocysteine were recently reported.[5] The inhibition of enzymes of homocysteine removal by uraemic toxins is a potential explanation. Hyperhomocysteinemia in ESRD maybe associated with decreased remethylation pathway in homocysteine metabolism.[18]

The pathologic mechanisms by which homocysteine promotes atherosclerosis remain unclear. Experimental data support a range of possibilities, including endothe-

lial cell injury, enhanced LDL oxidation, increased thromboxane-mediated platelet aggregation, inhibition of cell surface thrombomodulin expression and protein C activation, enhancement of lippoprotein(a)-fibrin binding, and promotion of smooth muscle cell proliferation. The *in vivo* relevance of findings from such experimental studies, however, has been seriously questioned due to their lack of specificity to homocysteine versus other much more abundant plasma thiols and the use of grossly supraphysiologic concentrations or nonphysiologic forms of reduced homocysteine.[5] Atherogenic effect and or prothrombotic effects of homocysteine has not been established.[19]

In this study, the only factor that correlated independently with total homocysteine concentration in non-diabetic ESRD patients was folic acid intake. Almost all studies shows an inverse correlation between folate levels and total homocysteine concentrations. Folate, vitamin B_6, and vitamin B_{12} were major determinants of plasma homocysteine.[20] There is a strong inverse correlation with folate levels, and weaker correlations with vitamin B_6 or vitamin B_{12}.[18] In ESRD patients, however, plasma levels of folate and vitamin B are generally adequate, reflecting the widespread use of supplements,[13] but normal plasma homocysteine concentrations were achieved in only a small number of patients.[9,13,21] There are some indications that folate metabolism is altered in renal failure.[18] Although plasma homocysteine concentrations in normal subjects can often be normalized by low doses of folic acid, such reductions have not been consistently achieved with up to 15 mg of folic acid per day in patients with ESRD.[9] Presently, data from uncontrolled interventional studies do not support the need for folate supplementation at doses above 5 mg per day. There appears to be no further benefit in supplementing vitamins B_6 and B_{12} at doses greater than those contained in the routine vitamin formulations currently recommended for ESRD patients on dialysis.[22]

In this study, total homocysteine concentrations in normal controls tend to be higher than several studies in different areas in Indonesia (Jakarta and Bali), which have mean values of 13.1±3.6 µmol/L,[23] 11.7±3.2 µmol/L,[24] and 10.7±3.4 µmol/L.[25] This difference may be due to differences in subject selection. In this study, all normal controls were paired with ESRD patients, with ages ranging from 43 years to 75 years. As determinants of homocysteine, the influence of age to plasma homocysteine concentration need to be accounted for this difference.[6]

However, all normal controls in this study have not been using folic acid or vitamin B in the past six months. Although in this study no measurements for folate levels and vitamin B concentrations were performed, according to results of the studies in Jakarta and Bali, which have mean values of folate levels 6.1±2.4 nmol/L[23] and 9.9±3.4 nmol/L,[24] there is a high probability that the normal controls in this study suffered from folate deficiency.

Nevertheless, we can conclude that this study shows that folic acid intake from daily food consumption may be not sufficient to preserve low levels of homocysteine concentration.

Another probability that could account for the difference in total homocysteine concentration in this study is the common polymorphisms in the methylenetetrahydrofolate reductase (MTHFR) gene, which has a relatively high frequency and shows a very heterogeneous distribution among different ethnic groups.[26]

In this study, factors that associated independently with total homocysteine concentrations in normal controls were increasing age and smoking habit. Plasma homocysteine concentrations increase with age. The homocysteine elevation with age might have resulted from an age-related decline in cystathionine-b-synthase and possibly other involved enzymes.[27] Besides that, marginal folate and other vitamin deficiencies known to be common in the elderly are likely to be contributing factors to hyperhomocysteinemia.[6]

Several studies demonstrated an association between smoking habit and homocysteine concentration.[28,29] The mechanism for elevated plasma homocysteine concentrations observed in smokers is not completely understood.[28] Cigarrette smoking could promotes the formation of abundant reactive oxygen species, which interfere with the synthesis of pyridoxal phosphate (vitamin B_6), and in turn increase homocysteine concentration. These results suggest another important mechanism, where smoking may promote atherogenesis.[20]

Several limitations to this study include the fact that the diagnosis of CAD in ESRD patients was only based on medical record review, ECG and echocardiographic criteria, which means that only patients with significant CAD were diagnosed. Besides that, in this study, neither examinations for folate levels, vitamin B_6, vitamin B_{12}, nor genetic analysis were performed.

Presently, there is no data demonstrating a reduction in CAD outcomes with successful treatment of hyperhomocysteinemia,[30-31] and the screening and treatment recommendations for hyperhomocysteinemia are premature.[5,32] Despite that, routine supplementation with regular doses of folic acid and vitamin B in ESRD patients is an easy, inexpensive, low risk, and probably beneficial action.

Prospective studies is needed to confirm the role of homocysteine as a predictor of cardiovascular events.

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