Original Article

Prevalence of Hyperhomocysteinemia in Thai CKD Patients and Relationship to Cardiovascular Events: Subgroup Analysis from Thai SEEK Study

Thananda Trakarnvanich MD[1], Atiporn Ingsathit MD[2],
Ammart Chaipresert MD[3], Prapaipim Thirakupt MD[4], Dhavee Sirivongs MD[5]

[1] Renal Division, Department of Medicine, Faculty of Medicine, Vajira Hospital, Navamindradhiraj University, Bangkok, Thailand
[2] Section for Clinical Epidemiology and Biostatistics, Research Center, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand
[3] Division of Nephrology, Department of Medicine, Phramongkutklao Hopsital, Bangkok, Thailand
[4] Division of Nephrology, Department of Pediatrics, Phramongkutklao Hospital, Bangkok, Thailand
[5] Division of Nephrology, Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand

Objective: It is well recognized that patients with chronic kidney disease [CKD] have an increased risk for cardiovascular disease [CVD]. Hyperhomocysteinemia appears to be a predictor of future CVD events. The prevalence of hyperhomocysteinemia in Thai CKD patients by using the Thai Screening and Early Evaluation of Kidney Disease [SEEK] study database and its relationship to CVD were studied.

Materials and Methods: Ninety-eight subjects were randomly sampled from the Thai SEEK study database. Traditional risk factors for CVD were examined and recorded. Stored sera of the subjects were analyzed for their total homocysteine [tHcy] level and its association with CKD and CVD.

Results: 72 subjects with CKD stage I-IV and 26 subjects without CKD were included. Fourteen subjects (14.3%) had CVD. Ten of them were in CKD stage III or higher. Only older age, CKD stage III, or elevated urine albumin/creatinine ratio (>300 mg/g) were associated with the presence of CVD. Mean plasma tHcy of only stage IV CKD, but not in the other stages, was significantly higher than in non-CKD group (14.56$\pm$7.96 µmol/L vs. 8.68$\pm$8.75 µmol/L, p = 0.016). Plasma tHcy level (>15µmol/l) was not associated with CVD or its risk factors. Only older age, CKD stage III or more and high urine albumin/creatinine ratio (>300 mg/g) were associated with the presence of CVD.

Conclusion: Hyperhomocysteinemia is more prevalent in advanced stage CKD. Traditional factors are not related to tHcy levels. CKD stages, older age and higher urine albumin-creatinine ratio were associated with CVD. Hyperhomocysteinemia may have an indirect relationship to development of CVD in later CKD stage.

Keywords: Hyperhomocysteinemia, Chronic kidney disease, Cardiovascular disease

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Cardiovascular disease [CVD] is the leading cause of death among patients with chronic kidney disease [CKD][1]. An elevated plasma concentration of homocysteine [tHcy] has been suggested as a new important risk factor for CVD[2,3], A previous study demonstrated that plasma tHcy increased progressively when renal function declined[4]. The prevalence of hyperhomocysteinemia is over 80% among dialysis patients[5] and mostly the level is over 15 µmol/L[6]. Nevertheless, little is known about the status of tHcy

Correspondence to:
Trakarnvanich T. Renal Division, Department of Medicine, Faculty of Medicine, University of Bangkok Metropolis, Bangkok 10300, Thailand.
Phone: +66-81-4431628, **Fax:** +66-2-2443469
E-mail: thananda@hotmail.com, thanandat@gmail.com

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levels in early stages of CKD, their relationship to CVD[7] and its traditional risk factors (lipid profiles, sex, and smoking). We therefore investigated the prevalence of hyperhomocysteinemia in Thai CKD patients by using the database of 3,459 Thai adult population from the Thai Screening and Early Evaluation of Kidney Disease [Thai-SEEK study] which is a community-based cross-sectional survey that was conducted between August 2007-June 2008 in four regions of Thailand determining CKD prevalence and risk factors[8].

Materials and Methods

Ninety-eight subjects from CKD stages 3 to 4 were randomly sampled from the Thai-SEEK study database. The database in the protocols included: personal history of age, religion, occupation, education level, and income; history of smoking, alcohol consumption, and exercise; history of cardiovascular events, diabetes; and physical findings of weight, height, systolic and diastolic blood pressure. The study was approved by the Local Ethical Board Committee.

Statistical analysis

Continuous data were expressed as mean ± standard deviation. Categorical variables were described using number and percentage. Mean levels of tHcy were compared between CKD groups by analysis of variance [ANOVA]. Multiple comparisons by Scheffe's method was used to compare more than 2 groups with CKD. Multiple logistic regression analysis was used to determine the factors associated with CVD. All analyses were performed using SAS. The *p*-value <0.05 was considered significant.

Results

Baseline characteristics of 98 patients are listed in Table 1. Slightly more than half of the study population were female (52%). The mean age was 53.8± 17.07 years and a glomerular filtration rate (GFR) of 73±33.0 mL/ min per 1.73m^2. CKD was stage I in 17.4%, stage II in 15.3%, stage III in 28.6%, and stage IV in 12.2% . Mean levels of tHcy were 8.7± 2.09 µmol/L in non-CKD and 10.0 ±3.98 µmol/L,10.1±2.85 µmol/L, 11.4±6.29 µmol/L, 14.6±7.96 µmol/L in CKD stage I, II, III and IV respectively (Figure 1).

Hyperhomocysteinemia was not found in non-CKD subjects. The prevalence of hyperhomocy steinemia increased as stage advanced: 11.8% in CKD stage I, 13.3% in stage II, 14.3% in stage III, and 33.4% in stage IV. Mean plasma tHcy in CKD stage IV was significantly higher than in the non-CKD group

Table 1. Demographic data (n = 98)

Characteristics	n (%)
Age (year)	
<40	23 (23.47)
40 to 59	35 (35.71)
>60	40 (40.82)
Mean (SD)	53.78 (17.07)
Median (minimum-maximum)	57.50 (20 to 89)
Sex	
Male	47 (47.96)
Female	51 (52.04)
Religion	
Buddhist	93 (94.90)
Christian	1 (1.02)
Muslim	4 (4.08)
Marital status	
Single	11 (11.22)
Married	72 (73.47)
Divorced	3 (3.06)
Widowed	12 (12.24)
Education	
None	6 (6.12)
Primary	66 (67.35)
Secondary	17 (17.35)
Diploma	5 (5.10)
Bachelor's degree	3 (3.06)
Occupation	
Agriculture	39 (39.80)
Government officer/business	11 (11.22)
Laborer	9 (9.18)
Housewife	10 (10.20)
Unemployed	10 (10.20)
Employee	8 (8.16)
Retired	4 (4.08)
Cattle rancher	2 (2.04)
Student	1 (1.02)
Others	4 (4.08)
Income (baht)	
≤2000	14 (14.29)
2,001 to 5,000	28 (28.57)
5,001 to 10,000	22 (22.45)
10,001 to 15,000	11 (11.22)
≥15000	20 (20.41)
No income	3 (3.06)
Smoking history	
Current smoker	25 (25.51)
Ex-smoker	17 (17.35)
Never smoked	56 (57.14)
Regular exercise	
Yes	53 (54.64)
No	44 (45.36)
Alcohol	
Current	40 (40.82)
Ex-drinker	13 (13.27)
Never	45 (45.92)

(14.6±7.96 µmol/L vs. 8.7±8.75 µmol/L, $p = 0.016$) but not different from other CKD stages.

Factors associated with hyperhomocysteinemia and cardiovascular disease

There were no association between plasma tHcy and life style behaviors such as smoking, drinking or physical activity, age, sex, or history of hypertension, diabetes mellitus, BMI, lipid profile, and urine albumin to creatinine ratio (Table 3). However, plasma tHcy increased significantly with CKD stage IV. Fourteen subjects (14.3%) had CVD, ten of them were in CKD stage III or more. There was no significant association between plasma tHcy and CVD. Only older age, CKD stage III or increased urine albumin/creatinine ratio (300 mg/g) were associated with the presence of CVD (Table 4).

In order to determine the factors that could help predict CVD, multiple logistic regression analysis was used. We found that CKD stages III-IV ($p = 0.012$) and urine albumin/creatinine ratio ($p = 0.014$) were significantly associated with history of CVD (Table 5).

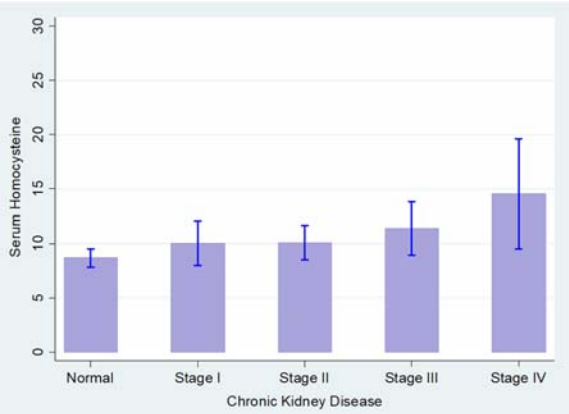

Figure 1. Mean level of homocysteine in each CKD stage.

Discussion

An elevated plasma homocysteine has been suggested to be a novel risk factor for cardiovascular disease [CVD] in general population[9] . A 3 µmol/L increase in tHcy enhanced the risk of CVD by 11% and stroke by 20%[10]. In healthy individuals, plasma tHcy level is between 5 to 10 µmol/L. Hyperhomocysteinemia has been categorized into 3 groups: moderate (16 to 30 µmol/L), intermediate (31 to 100 µmol/L), and severe (>100 µmol/L)[11].

There are still conflicting results regarding the potential role of tHcy as a causal factor of atherosclerosis. The association of tHcy concentration and atherosclerosis with CVD may vary between population and geographical area. We studied the CKD population from the Thai SEEK study which was a large population-based study in four parts of Thailand. The present study which found the highest prevalence of hyperhomocysteinemia in the stage IV CKD was consistent with previous studies. However plasma tHcy was not related to other traditional risk factors such as lipid profiles. This emphasizes that tHcy may be not associated with classical risk factors. The current information also showed that less than 50% of cardiac patients present with classical risk factors[12,13] but this only partly explains the risks factors for CVD. In our study, we found no significant association between plasma tHcy and CVD. In addition, the influence of lipid and CVD appears to demonstrate a u-shaped relationship, with increased CVD events among advanced CKD patients having low cholesterol[14]. The apparent non-association between plasma tHcy and CVD in this study may be partly explained from the small elevation of tHcy in each CKD group.

Mean levels of plasma tHcy were just above the normal limits of the definition of hyperhomocy

Table 2. Homocysteine levels by CKD stages

CKD Stage	Number (%)	Mean (SD)	Median (Min-Max)	95% CI
Normal	26 (26.53)	8.68 (2.09)	8.75 (5.17 to 13.10)	7.83 to 9.52
Stage I	17 (17.35)	10.04 (3.98)	9.69 (3.61 to 20.50)	7.99 to 12.08
Stage II	15 (15.31)	10.08 (2.85)	10.20 (6.17 to 15.80)	8.50 to 11.65
Stage III	28 (28.57)	11.39 (6.29)	9.98 (5.80 to 38.00)	8.95 to 13.83
Stage IV	12 (12.24)	14.56 (7.96)*	11.78 (5.00 to 34.70)	9.50 to 19.62

By using the Analysis of Variance (ANOVA), the mean level of Homocysteine in each CKD stage is significantly different (p-value = 0.016), and when using multiple comparison with Sheffe's method, the mean level of homocysteine in CKD stage IV was significantly higher than in the normal group (p-value = 0.024)

Table 3. Factors associated with homocysteine level

Factors	Homocysteine >15 (n = 12)	Homocysteine <15 (n = 86)	*p*-value
Urine microalbumin group			0.697*
≤30	9 (11.39)	70 (88.61)	
>30	3 (15.79)	16 (84.21)	
HDL			1.000
M >40, F >50	5 (11.63)	38 (88.37)	
M ≥40, F ≤50	7 (12.73)	48 (87.27)	
Hypertension			0.293*
No	7 (9.72)	65 (90.28)	
Yes	5 (19.23)	21 (80.77)	
Diabetes mellitus			0.680*
No	10 (11.90)	74 (88.10)	
Yes	2 (14.29)	12 (85.71)	
Smoker			0.824
Smoker	6 (14.29)	36 (85.71)	
Never	6 (10.71)	50 (89.29)	
Alcohol			1.000
Current	6 (11.32)	47 (88.68)	
Never	6 (13.33)	39 (86.67)	
Exercise			0.203
Yes	4 (7.55)	49 (92.45)	
No	8 (18.18)	36 (81.82)	

* Fisher's exact test

steinemia. Our findings indicated that the level of tHcy in Thai CKD patients is rather low compared to other ethnic groups, and the association between hyperhomocysteinemia and CVD is independent.

We found factors associated with CVD were older age, CKD stages III or above, and high urine albumin/creatinine ratio (300 mg/g). The incidence of CVD in our population was quite low. The strength of association of plasma tHcy concentrations and atherosclerosis may vary between populations. Thus the relationship between tHcy and CVD in our CKD group was indirectly linked to advance CKD stages. As the patients get older, the prevalence of CKD is higher as is the incidence of atherosclerosis and CVD[15]. This is consistent with the results of the Thai SEEK study which found that prevalence of CKD is higher with increasing age. Our study also found that microalbuminuria had a significant relationship with CVD. The link between albuminuria, CVD and progressive renal disease is now well established in the general population and in patients with diabetes mellitus[16]. Albuminuria and renal impairment provide additional and independent risks for cardiovascular mortality[17]. Data from the National Health and Nutrition Examination Survey [NHANES] revealed that the prevalence of proteinuria increased with age above 40 years[18,19]. have shown that hyperhomocysteinemia is an independent risk factor for the development of microalbuminuria in type 2 diabetes. Therefore, plasma tHcy may be indirectly linked to CVD by correlation with albuminuria.

Conclusion

Our data demonstrated that plasma tHcy is higher in advanced CKD stages especially stage III onwards. Although plasma tHcy cannot predict CVD in this study, it may have an indirect relationship to development of CVD especially in later stages.

What is already known on this topic?

Chronic kidney disease [CKD] have an increased risk for cardiovascular disease [CVD]. Hyperhomocysteinemia appears to be a predictor of future CVD events.

What this study adds?

The prevalence of hyperhomocysteinemia in higher in Thai patients with advanced stage CKD. CKD

Table 4. Factors associated with cardiovascular disease

Factors	History of cardiovascular disease (n = 14)	No history of cardiovascular disease (n = 84)	*p*-value
Age (year), mean (SD)	63.21 (14.02)	52.18 (17.10)	0.024
Sex			0.201
Male	4 (8.51)	43 (91.49)	
Female	10 (19.61)	41 (80.39)	
BMI			0.648
Normal	9 (16.67)	45 (83.33)	
Overweight+	5 (11.36)	39 (88.64)	
CKD			0.026
Normal and stage I-II	4 (6.90)	54 (93.10)	
Stage III-IV	10 (25.00)	30 (75.00)	
TG			0.707
<150	7 (17.07)	34 (82.93)	
≥150	7 (12.28)	50 (87.72)	
CHOL			0.149
<200	4 (8.16)	45 (91.84)	
≥200	10 (20.41)	39 (79.59)	
LDL			0.765*
<100	4 (11.76)	30 (88.24)	
≥100	10 (15.63)	54 (84.38)	
Urine albumin/cr group			0.027*
≤300	8 (10.13)	71 (89.87)	
>300	6 (31.58)	13 (68.42)	
Urine microalbumin group			0.138*
≤30	9 (11.39)	70 (88.61)	
>30	5 (26.32)	14 (73.68)	
HDL			0.708
M >40, F >50	5 (11.63)	38 (88.37)	
M ≤40, F ≥50	9 (16.36)	46 (83.64)	
Hypertension			1.000*
No	10 (13.89)	62 (86.11)	
Yes	4 (15.38)	22 (84.62)	
Diabetes mellitus			0.416*
No	11 (13.10)	73 (86.90)	
Yes	3 (21.43)	11 (78.57)	
Smoking			0.771
Current/ex-smoker	5 (11.90)	37 (88.10)	
Never smoked	9 (16.07)	47 (83.93)	
Alcohol drinking			0.075
Current	4 (7.55)	49 (92.45)	
Never	10 (22.22)	35 (77.78)	
Regular exercise			0.622
Yes	9 (16.98)	44 (83.02)	
No	5 (11.36)	39 (88.64)	
Homocysteine			1.000*
<15	13 (15.12)	73 (84.88)	
≥15	1 (8.33)	11 (91.67)	

* Fisher's exact test

stages, older age and higher urine albumin-creatinine ratio were associated with CVD. Hyperhomocysteinemia may have an indirect relationship to development of CVD in advanced stage CKD.

Table 5. Multiple Logistic Regression Analysis, Relation between Cardiovascular events and CKD stages and Urine albumin/creatinine ratio

Factors	Adjusted OR	95% CI of adjusted OR	*p*-value
CKD stage III-IV	1.71	1.46 to 20.81	0.012
Urine albumin/cr >300	1.67	1.40 to 19.97	0.014

* Reference group: Normal and CKD stage I-II, Urine albumin/cr ≤300

Potential conflicts of interest

The authors declare no conflict of interest.

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