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SERUM HOMOCYSTEINE CONCENTRATIONS INVERSELY CORRELATES TO INTIMA-MEDIA THICKNESS OF CAROTID ARTERIES: AN IMPACT TO ENVERSE EPIDEMIOLOGY IN PRE-DIALYTIC CHRONIC KIDNEY DISEASE

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Background: In normal population, serum homocysteine (Hcy) is considered as a marker of atherosclerotic and cerebro-cardiovascular diseases. It is not clear whether this phenomenon also occurs in chronic kidney disease particularly among pre-dialytic population. This study aims to determine relationship between serum Hcy concentrations and carotid arteries intima-media thickness (CA-IMT) of pre-dialytic chronic kidney disease (CKD) patients. **Method:** A cross-sectional study was carried out on pre-dialytic CKD patients. Morning fasting blood samples were taken for lipid profile, blood sugar, blood urea nitrogen, serum creatinine concentrations. Total fasting serum Hcy concentrations were measured using chemiluminescent assay. CA-IMT of patients were measured by USG B-Mode Logiq-5 (General Electric), with 7.5 MHz linear transducer at both left and right, common and bifurcation of carotid arteries. **Results:** Ninety (74 males, 16 females) of pre-dialytic patients, age 54 ± 7 years, SBP 137±20 mmHg, DBP 78±13 mmHg, BMI 23.9±4.4 kg/m2 FBS 94±16 mg/dL and 2h pp BS 125±31 mg/dL, total-C 201±65 mg/dL, LDL-C 129±62 mg/dL, HDL-C 40±13 mg/dL, TG 144±81 mg/dL, phosphate 3.8±1.3 mg/dL, calcium 8.7±1.1, and CaXP 32±8, and total serum Hcy 17.11±6.91 µmol/L, e-GFR (CG formula) 36±17 ml/minutes were included in this study. There were significant negative correlation between Hcy concentrations and left common CA-IMT (r = 0.28; B = -11.01; p = 0.02) and right bifurcation CA-IMT (r =0.26; B = -11.01; p=0.042). While there were a trend of negative correlation between total serum Hcy and right common CA-IMT (r= 0.21; B = -8.27; p=0.10) and left bifurcation CA-IMT (r= 0.20; B=-6.69; p=0.11). **Conclusion:** There is a negative association between total serum Hcy concentrations and atherosclerotic process in carotid arteries. The inverse relationship may support phenomenon of inverse epidemiology among pre-dialytic CKD patients and seemed that serum Hcy reflects nutritional marker rather than a marker of cardiovascular disease.

Keywords: serum, homocysteine, carotid, arteries, intima-media.

INTRODUCTION

Homocysteine (Hcy) is considered as a marker of cardiovascular disease. In a prospective study among ESRD patients, Bostom et al., found an association of total serum Hcy concentrations with cardiovascular outcomes.[1] After controlling for some variables, Hcy was found a 3.0- to 4.5-fold increased incidence of pooled fatal and nonfatal cardiovascular events. However in an other prospective study which was evaluated relationship between plasma thiols levels and cardiovascular events at the initiation of dialysis in chronic renal failure patients[2].This study shows that, at the initiation of dialysis in patients with late-stage chronic renal failure it was reported that plasma total Hcy concentrations in the group with cardiovascular disease was significantly lower than plasma tHcy in patients without cardiovascular disease. These findings suggest that higher plasma total Hcy concentrations is protective against CVD in these patients, A similar finding also was reported in a study among patients initiating dialysis treatment. It was shown an inverse relationship between plasma total Hcy and all cause and cardiovascular mortality.[3] In ARIC study it was reported that CKD was associated with one and a half increased of atherosclerosis disease of peripheral vessel, although the risk is adjusted for other cardiovascular risk factors.[4]

Mechanism of reverse epidemiology may occurs among dialysis patients which shows association between plasma total Hcy concentrations and cardiovascular disease is reverse in particular among CKD patients. There is strong

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correlation between atherosclerosis and malnutrition and cardiovascular death, in CKD patients. On the other hand plasma Hcy is considered a marker of atherosclerosis and/or malnutrition. Atherosclerosis process is best observed in carotid arteries. Diagnostic validity of carotid ultrasonography cardiovascular outcome was studied in a cohort of more than one hundred thirty patients who were on maintenance dialysis therapy. At the end of follow-up, around a half of patients died due to cardiovascular events. IMT of common carotid arteries was significantly higher in patients who died of cardiovascular events than in patients who survived[5]. We therefore conducted a study to determine relationship between serum Hcy concentrations and carotid arteries intima-media thickness (CA-IMT) of pre-dialytic CKD patients

PATIENTS AND METHOD

A cross-sectional study was done on pre-dialytic CKD patients. Patients who visited out-patient clinics aged 18-60 years and estimated glomerular filtration rate (e-GFR) less than 60 mL/minutes/ 1.73 m^2. All patients were signed inform concern and ethical clearance were obtained from local ethical commission board. All clinical treatments were free of malpractice.

Patients with history of kidney transplant and hemodialysis treatment, coronary artery disease, peripheral arterial disease and stroke were excluded from the study. Those who were eligible were consecutively recruited as study subjects. Morning fasting blood samples were taken for lipid profile, blood sugar, blood urea nitrogen, serum creatinine concentrations. Serum total fasting Hcy concentrations were measured using chemiluminescent assay. Carotid artery intima-media thickness (CA-IMT) of patients were measured by USG B-Mode Logiq-5 (General Electric), with 7,5 MHz linear transducer at both left and right, common and bifurcation of carotid arteries. IMT was measured as maximum distance between liminal-intimal and media-adventitia. USG examination was done by a radiologist. CA-IMT were done manually using USG B-mode at 12 locations of distal segments of carotis communis, bifurcatio and proximal segment left and right internal carotis.

Descriptive statistics was performed to describe patients characteristics. Pearson's correlation and simple regression analysis was applied to analyze the relationship between serum Hcy concentrations and carotid arteries intima-media thickness (CA-IMT). Significant was considered probability (*p*) value less than 0.05

RESULTS

During the study, ninety (74 males, 16 females) of pre-dialytic patients, age 54 ± 7 years, SBP 137±20 mmHg, DBP 78±13 mmHg, BMI 23.9±4.4 kg/m2 FBS 94±16 mg/dL and 2h pp BS 125±31 mg/dL, total-C 201±65 mg/dL, LDL-C 129±62 mg/dL, HDL-C 40±13 mg/dL, TG 144±81 mg/dL, phosphate 3.8±1.3 mg/dL, calcium 8.7±1.1, and CaXP 32±8, and total serum Hcy 17.11±6.91 µMmol/L, e-GFR (CG formula) 36±17 ml/minutes were included in this study (Table 1).

Table1
Relationship between independent variables (t-Hcy, total-C, LDL-C, HDL-C, TG, PO4, and BMI) right bifurcation CA-IMT among pre-dialytic CKD patients

Independent variables	B	SE(B)	Beta	T	*p*
t-Hcy (every 1 µmol/L increase)	-0.008	0.004	-0.252	-1.92	0.06
Total-C (every 1 mg/dl increase)	-0.002	0.001	-0.786	-2.34	0.02
LDL-C (every 1 mg/dl increase)	0.002	0.001	0.814	2.49	0.01
HDL-C (every 1 mg/dl increase)	0.001	0.002	0.055	0.40	0.69
TG (every 1 mg/dl increase)	0.001	0.001	-0.113	-0.83	0.41
PO_4 (every 1 mg/dl increase)	-0.010	0.018	-0.074	-0.55	0.58
BMI (every 1 kg/m2)	-0.004	0.06	-0.078	-0.06	0.56

CA-IMT (every 1 mm increase) is a dependent variable, R multivariate=0.45; rsq=0.21

There were significant negative correlation between Hcy concentrations and left common CA-IMT (r = 0.28; B -11.01; p = 0.02), see Figure 1 and right bifurcation CA-IMT (r =0.26; B = -11.01; p=0.042), see Figure 2.

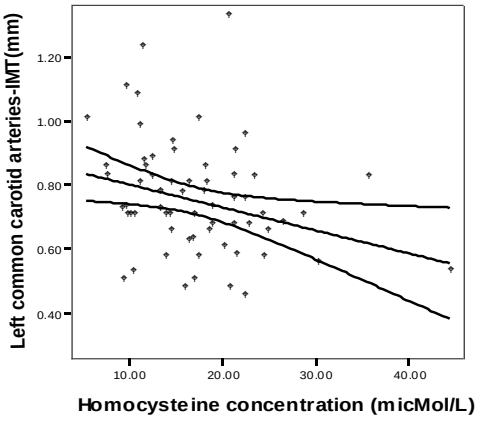

Figure1
There were significant negative correlation between Hcy concentrations and left common CA-IMT (r = 0.28; B -11.01; *p* = 0.02)

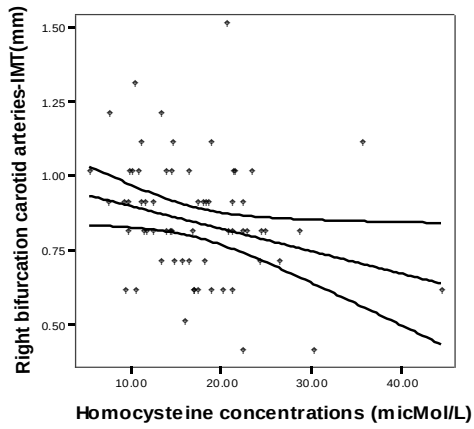

Figure 2
There were significant negative correlation between Hcy and right bifurcation CA-IMT (r =0.26; B = -11.01; *p*=0.042).

While there were a trend of negative correlation between total serum Hcy and right common CA-IMT (r= 0.21; B= -8.27; *p*=0.10), and left bifurcation CA-IMT (r= 0.20; B=-6.69; *p*=0.11), see Figure 3 and 4.

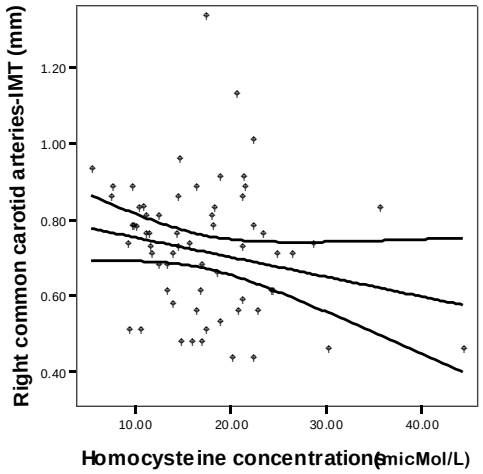

Figure 3
There were a trend of negative correlation between total serum Hcy and right common CA-IMT (r= 0.21; B -8.27; *p*=0.10).

Multivariate analysis showed that after adjustment for total cholesterol and LD-cholesterol, HDL-cholesterol, triglyceride, and phosphate concentrations, body mass index as some nutritional parameters, total Hcy concentration failed to associate with CA-IMT and in fact total-cholesterol and LDL-cholesterol concentrations were independent factors. It can be interpreted that total Hcy concentrations was a confounding factor for CA-IMT and considered associated with other nutritional parameters such as total-cholesterol and HDL-cholesterol concentrations.

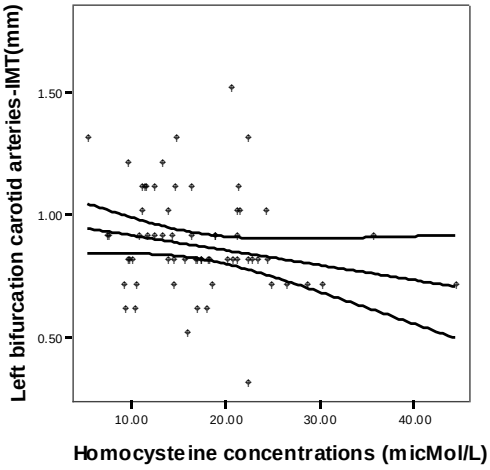

Figure 4
There were a trend of negative correlation between total serum Hcy and left bifurcation CA-IMT (r= 0.20; B=-6.69; *p*=0.11)

DISCUSSION

Our study has shown that a negative significant correlation between CA-IMT and plasma total concentration of Hcy in two locations namely left common CA-IMT and right bifurcation, meanwhile, a trend of negative correlation found in two location namely right common and left bifurcation. This finding means that the higher plasma total Hcy concentrations, the lower intima-media thickness found among pre-dialytic subjects in this study. It is unclear whether plasma-Hcy as a marker of nutritional status or cardiovascular outcome. This study seemed to support the role of Hcy as a marker of nutritional status.

Among normal individuals, obesity produced increased cardiovascular morbidity and mortality. In contrary, the effect of overweight or obesity in CKD patients with regular hemodialysis was in the reverse direction; i.e. obesity is associated with longer survival. This "reverse epidemiology" of obesity is relatively specific in regular HD patients. In peritoneal dialysis and pre-dialysis the association between BMI and mortality are varies. This finding may resulted in inconsistent opinion among author about whether or not to treat obesity on CKD patients.[6] Kovesdy et al., has reported reverse correlation between lipids concentrations and mortality among males with pre-dialytic CKD. It was found that lower total cholesterol is associated with higher mortality after adjusted for age, race, body mass index. Similar association was found between plasma HDL-cholesterol and triglyceride concentrations and cardiovascular and all cause mortality.[7] Our similar results also revealed that total Hcy concentration

failed to associate with CA-IMT after adjustment for total cholesterol and LD-cholesterol, HDL-cholesterol, triglyceride, and phosphate concentrations, body mass index as some nutritional parameters, and the analysis has showh that total-cholesterol and LDL-cholesterol concentrations were independent factors. It can be interpreted that total Hcy concentrations was a confounding factor for CA-IMT and considered associated with other nutritional parameters such as total-cohesterol and HDL-cholesterol concentrations.

Variation of the association can be "very different" (association between systolic and diastolic blood pressure and mortality) until mirror image (association between BMI and mortality). These differences in association may be due to effect of confounding factors of protein-energy malnutrition and inflammation in CKD and dialysis patients. Especially in obese patients, hemodynamic factors, plasma cytokines, neurohormonal and interaction of endotoxin-lipoprotein, and malnutrition-inflammation complex syndrome may affect the "different association". Combination between protein-energy malnutrition, chronic inflammation conditions and oxidative stress especially carbonyl stress may responsible on this reverse epidemiology.[8] In peritoneal dialysis (PD) patients a cohort study among 61 patients was reported non-specific inflammation and age plays a role in the progression of atherosclerosis.[9]

In more than three hundreds end-stage renal disease patients who starting dialysis therapy. It was revealed that patients with lower plasma Hcy concentrations had significantly higher cardiovascular morbidity and mortality. Multivariate analysis showed that after controlling for some confounding factors, CV mortality remain consistently associated with low plasma Hcy. If controlled by nutritional and inflammation parameter of BMI (body mass index), SGA (subjective global assessment), serum creatinine, serum albumin and CRP, however, a low plasma total Hcy concentrations was no longer associated with higher mortality although, a trend for high plasma total homocystein concentrations was observed. In This study, it was also shown that low cholesterol concentrations may reflect energy malnutrition and was confounded by lower Hcy concentrations as it was shown by multivariate analysis, that is low cholesterol concentrations associated with increased CA-IMT. It seemed that relationship between malnutrition inflammation and a low plasma total Hcy is responsible for the reverse association between plasma total Hcy concentration and cardiovascular outcome in renal failure patients. Confounding factors including nutritional and inflammation parameters, tend increased death risk for high, rather than low Hcy levels which was apparent after statistical Adjustment.[10] Reverse association between some nutritional factor and mortality may affect the management of CKD patients, however, it is still need to ascertain whether improvement such nutritional parameters will improve mortality, improve survival and quality of life.[11]

Our study shows that there is reverse association between serum total Hcy and CA-IMT, however, it is confounded by cholesterol concentrations as a marker of energy malnutrition. These findings may explain the high incidence of cerebrovascular disease in kidney failure with regular hemodialysis who suffered malnutrition. It implicates reverse epidemiology in CKD patients and whether nr not to treat obesity in CKD patients with hemodialysis.

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Conflict of interest statement.
None conflict interest to be stated

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