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The proportion hyperhomocysteinemia in chronic kidney disease patients

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ABSTRACT

Background: Chronic kidney disease (CKD) patients often have a high homocysteine level Hyperhomocystinemia considered as one of cardiovascular disease risk factor in CKD patients. Studies concern on the proportion of hyperhomocysteinemia in patients with CKD in Indonesia are very limited. **Aims and Objectives:** The main objective was to identify the proportion of hyperhomocysteinemia in CKD patients. **Materials and Methods:** This was a cross sectional study. Subjects in this study were CKD patients with routine hemodyalisis two times per week. Five mililiters venous blood was collected before the first hemodyalisis. The blood was stored into tubes contain clot activator. Homocysteine level higher than 15.39 μmol/L considered as hyperhomocysteine. **Results:** Total of 122 subjects included at this study. Subjects dominated by male with mean age of 51.7 years. Anemia (86.9%) and hypertension (86.1%) were the common comorbidities. Co-treatment assessed in this study i.e.: folic acid, calcium carbonat, antihypertensive agent, antidiabetic agent, antiplatelet agent, lipid lowering agent, and hematopoietic agent. The prevalence of hyperhomocysteinemia was high (89.3%) despite of the high consumption of folic acid in subjects (86.1%). **Conclusion:** Hyperhomocysteinemia is a common condition among CKD patients with hemodyalisis.

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INTRODUCTION

Chronic kidney disease (CKD) defined as structural and functional disfunction and/or decreasing in glomerulus filtration <60 mL/minutes/1.73m^2 that lasting for more than 3 months.[1] CKD is a major health problem for the countries of Southeast Asia, including Indonesia.[2] As the growing elderly population and increasing numbers of patients with diabetes and hypertension, the numbers of CKD patients will continue to rise and primary care practitioners will be confronted with management of the complex medical problems unique to patients with CKD.[3]

The risk for cardiovascular disease (CVD) morbidity and mortality remains high in all stages of CKD,[4] including in patients with hemodialysis.[5,6] More patients with CKD die of CVD than of the progression of kidney failure.[7] The increase of homocysteine level, referred as hyperhomocysteinemia, is highly prevalent in CKD patients[8] and associated with an increased risk of CVD complications.[9-11]

Homocysteine, a sulfur amino acid, is the only direct precursor for l-methionine synthesis.[12] Hyperhomocysteinemia can also arise from nutritional deficiencies of folate, vitamin B_6, and vitamin B_{12}.[13] Folic acid, vitamin B_6, and B_{12} are essential cofactors in homocysteine-methionine metabolism. Therefore, low vitamin B availability (B_6, B_{12} and folic acid) impaired re-methylation of homocysteine to methionine and leads to homocysteine accumulation.[14] Vitamin deficiency (including vitamin B_1, B_6, B_{12}, and folic acid) are common in people with advanced renal failure who do not take nutritional supplements.[15,16] This factor thought to be one of the reason of the high prevalence oh hyperhomocysteinemia in CKD patients.Studies

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concern on the proportion of hyperhomocysteinemia in patients with CKD in Indonesia are very limited. The objective of this study is to identify the proportion of hyperhomocysteinemia in CKD patients.

MATERIALS AND METHODS

The method of this study was a cross sectional study conducted at Bethesda Hospital and Panti Rapih Hospital, Yogyakarta, Indonesia from August to September 2018. Each subject would be followed for 4 weeks.

After sample calculation, the minimum subjects requirement were 120 subjects. Inclusion criteria i.e.: male or female, age >18 years, diagnosed with CKD. Each subject undergo a routine hemodyalisis two times per week (describe as "first hemodyalisis" and "second hemodyalisis" for the sequence of hemodyalisis per week) with time interval between each hemodyalisis was 3 to 4 days. Exclusion criteria i.e.: did not willing to join the study, participation in other clinical trial in the last 1 month, incompetent to give a consent and to answer the questionnaires, pregnant or has a plan to get pregnant.

Variables assessed in this study i.e.: demographic data, medical history, co-treatment, homocysteine level, and the presence of adverse event. Demographic data includes: age, gender, marriage status, educational degree, and occupation. Five mililiters venous blood was collected before the first hemodyalisis. Blood collection was done by nurse in hemodyalisis center and tested by laboratory technician in a certified laboratory. The blood was stored into tubes contain clot activator. Homocysteine level higher than 15.39 µmol/L considered as hyperhomocysteine.Subjects characteristics and the proportion of hyperhomocysteinemia were described in percentage.

Ethical clearance

Each subject participating in this study must signed an informed consent form. Informed consent process will be made very clearly. Each patient was freed to choose to be involved or not to be involved in this study. For those who refuse to be involved in this study are not required to explain their reason and will not affect their therapy.

The data used only for research. Patients identity will be classified. All document will be saved in study center after the study is completed. The research document will only be seen by the parties related to this research. This study was verified by Duta Wacana Christian University School of Medicine Ethical Research Committee with number of ethical clearance 614/C.16/FK/2018.

RESULTS

Total of 122 subjects included at this study, dominated by male with mean age of 51.7 years. Anemia (86.9%) and hypertension (86.1%) were the common comorbidities. Co-treatment assessed in this study i.e.: folic acid, calcium carbonat, antihypertensive agent, antidiabetic agent, antiplatelet agent, lipid lowering agent, and hematopoietic agent. Folic acid (86.1%) and hematopoietic agent (82.8%) were the common co-treatment. Table 1 shows the subjects' characteristics.

Figure 1 represent the proportion of hyperhomocysteinemia compared to normal homocysteine level. The prevalence of hyperhomocysteinemia was 89.3%. Despite of the high consumption of folic acid, the proportion of hyperhomocysteinemia in CKD patients remains high.

Table 1: Characteristics of subjects

Characteristics	Number of subjects (n=122)	%
Gender		
Male	78	63.9
Female	44	36.1
Mean age	51.7±12.6 years	
Comorbidity		
Hypertension	105	86.1
Diabetes Mellitus	41	33.6
Stroke	9	7.4
Cardiovascular disease	32	26.2
Congenital kidney disease	2	1.6
Urinary tract calculus	9	7.4
Urinary tract infection	5	4.1
Anemia	106	86.9
Dyslipidemia	4	3.3
Co-treatment		
Folic acid	105	86.1
Calcium carbonat	84	68.9
Antihypertensive agent	100	82
Antidiabetic agent	27	22.1
Antiplatelet agent	11	9.0
Lipid lowering agent	7	5.7
Hematopoietic agent	101	82.8

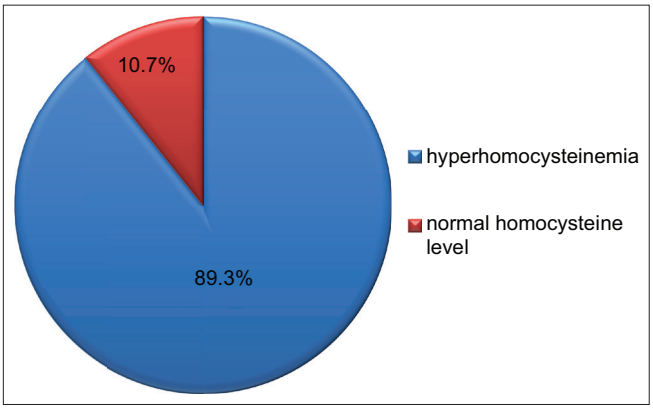

Figure 1: The proportion of hyperhomocysteinemia

DISCUSSION

Hyperhomocysteinemia defined as homocysteine level higher than 15.39 μmol/L. Hyperhomocysteinemia known as a common condition among CKD patients with hemodyalisis.[17] This present study was also showed a high prevalence of hyperhomocysteinemia. The prevalence of hyperhomocysteine was 89.3%. This result is similar to previous studies. Ciancolo, et al. (2017) stated hyperhomocysteinemia occurs in about 85% of CKD patients because of impaired renal metabolism and reduced renal excretion.[18] This statement is in concordance with Long and Nie (2016). Homocysteine level in patients with end-stage of renal disease (ESRD) is 3 to 5 times higher than normal and the prevalence of hyperhomocysteinemia in this patient group is 85-100%.[19] A cross sectional study by Chen, et al. (2017) in patients with CKD stage 2 to 5 showed hyperhomocysteinemia was prevalent. Homocysteine levels were 2-fold higher in hemodialysis patients than those in early stage CKD.[20] Cross sectional study included 1042 CKD patients showed the prevalence of hyperhomocysteinemia in CKD was increasing as the disease stage increase. The prevalence of hyperhomocysteinemia in CKD stage 1, stage 2, stage 3, stage 4 and stage 5 patients was 10.73%, 29.22%, 58.71%, 75.23% and 83.75%, respectively.[21]

CVD and stroke are the most common cause of death in the setting of ESRD.[22] Individuals with stage 3 CKD are more likely to die from CVD than to progress to ESRD.[23] One of the proposed mechanism of CVD in patients with CKD is the high homocysteine level. In a study on dialysis patients with and without CVD, serum homocysteine level was significantly high in patients with CVD compared to patients without accompanying CVD (37. 2 μmol/L versus 24 μmol/L). In other study performed on 176 patients with ESRD, patients with a greater serum level of homocysteine had 2.9 times higher rates of atherosclerosis and thrombotic events.[24]

Hyperhomocysteinemia induce induces oxidative stress and antagonizes the vasodilator properties of nitric oxide, thus leading to endothelial dysfunction. Following oxidative stress, endothelial cells produce various cytokines participating in inflammatory reactions.[18] Hyperhomocysteinemia activates metalloproteinases and induces collagen synthesis, leading to the reductionof vascular elasticity.[25] Homocysteine was also proven to promote the proliferation of smooth muscle cells leading to several interactions with platelets, clotting factors, lipids,[18] and indeed might contribute to the scavenger receptor-mediated uptake of oxidized-LDL by macrophages resulting in foam cell formation in atherosclerosis.[26]

Despite of the high consumption of folic acid, the proportion of hyperhomocysteinemia in CKD patients in this current study remains high. Proposed mechanisms for hyperhomocysteinemia in kidney failure include deficiencies of vitamin cofactors (pyridoxal 5'-phosphate/ PLP, an active form of vitamin B_6, B_{12}, and folic acid)[19,27] and reduced clearance of total plasma homocysteine.[28] The administration of vitamin B, especially vitamin B_6, vitamin B_{12}, and folic acid, are potential to reduce homocysteine level.[29-32]

CONCLUSION

This study shows hyperhomocysteinemia is common among CKD patients with hemodyalisis. Hyperhomocysteinemia is a risk factor for CVD complication in CKD patients and is commonly associated with deficiencies of vitamins B. Supplementation of vitamin B in CKD patients is higly recommended.

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RTP: Concept and design of study, reviewed the literature, collected data, prepared first draft of manuscript; **RDLRS:** Concept and design of study, reviewed the literature, literature search, manuscript preparation, statistically analyzed and interpreted, revision of the manuscript; **EAP:** Concept and design of study, collected data, prepared first draft of manuscript

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