Original article

THE ROLE OF NEOPTERIN AS A NOVEL BIOMARKER FOR REDUCED KIDNEY FUNCTION: A COMMUNITY BASED STUDY

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ABSTRACT

Cardiovascular disease is a major complication for patents with reduced kidney function. Neopterin is well known as a biomarker for cardiovascular disease, however it is not clear whether it is associated with reduced kidney function. Study was carried out in a Legian Kuta village a tourist town in Bali. Samples were underwent a series of interview, physical examination and were taken blood samples for neoperin and creatinine tests. Neoptein concentrations were tested for its normal distribution and associated with C-G formula for estimated glomerular filtration rate. Cut-off value for prediction of reduced renal function was rested using ROC curve, and calculated for sensitivity, specificity.

Seventy nine samples were selected through cluster random sampling from 284 residents (177 males and 107 females) with age 46 ± 10 years, body weight 67 ± 13 kg and height 162 ± 9 cm. It was shown that neopterin concentration was normally distributed (K-S Z = 1.175, p = 0.126), with mean 6.66 ± 3.35 ng/ml and e-GFR was 89 ± 25 ml/mnt. There was significant negatively correlation between neopterin concentrations and e-GFR (R = -0.26, Rsq = 0.068, p = 0.021), using regression equation it was revealed that every 1 unit increased of neopterin concentrations produce 1.42 decrease of e-GFR. Using ROC curve, neopterin was accurately detect reduced kidney function defined as e-GFR of 60 ml/mnt or less (AUC = 0.88; 95%CI 0.74 to 1.00; SE = 0.07; p = 0.02). Using 7.46 ng/ml as cut-off value for normal neopterin concentrations, it was showed that sensitivity and specificity were 100% and 72% to detect the presence of reduced kidney function, consecutively. Neopterin may be used as a novel biomarker for reduced kidney function, for its role in the pathogenesis of cardiorenal syndrome in general population.

Keywords: neopterin, reduced kidney function, general population, biomarker cardiorenal syndrome

INTRODUCTION

Neopterin a product of pteridine metabolism is impaired in uremic state. In renal failure, neopterin concentrations are increased because of impaired excretion as well as increased production of the compound due to systemic inflammation.[1] Neopterin is an independent predictor of all caused and cardiovascular mortality in individuals with and without stable coronary artery disease.[2] Avanzas, *et al*.[3] showed that increased serum neopterin predicts future adverse cardiac events in patients with chronic stable angina pectoris.

Cardiovascular diseases is a major complication for patents with reduced kidney function. The risk of CV death in patients with CKD (Chronic Kidney Disease) at the age of 40 years was 100 times higher than normal population.[4] CV death contributed around 20 – 23%

of annual mortality rate in United State.[5] Neopterin is produced by monocytes and macrophages in response to stimulation by interferon γ, a cytokine originating mainly from T-helper type-1 lymphocytes and natural killer cells.[6] Neopterin is formed by hydrolysis and oxidation of 7,8-dihydroneopterin triphosphate, which originates from the conversion of guanosine triphosphate by the action of guanosine triphosphate-cyclohydrolase I.[7,8] The amount of neopterin secreted in strongly related to the release of reactive oxygen radicals by cells, reflecting the level of oxidative stress caused by activation of the immune system.[9,10]

Although, neopterin is well known as a predictor for cardiovascular mortality, however it is not clear whether it is associated with early stage reduced kidney function. This study is aimed to identify the relationship between plasma neopterin concentrations and kidney function in the community.

MATERIAL AND METHODS

This study was carried out in a Legian Kuta village a tourist town in Bali. Legian village is a costal tourism area which located in a Kuta resort area, that located of southern part of Bali island (see figure 2). Recruitment of subjects was made using cluster random sampling via Banjar (subunit area of a village) of Legian Village via random sampling, and cluster sampling was made through residents an each banjar. Samples were underwent a series of interview, physical examination and were taken blood samples for neopterin and creatinine tests. Out of those 284 blood samples that have been taken, 79 were selected via simple random sampling for the examination plasma neopterin and plasma creatinine to calculate estimated glomerular filtration rate.

Neopterin concentrations were measured by enzyme link immunosorbant assays and creatinine concentrations were measured using Jaffe methods. Neoptein concentrations were tested for its normal distribution and associated with C-G (Cockcroft-Gault) formula for estimated glomerular filtration rate (estimated glomerular fikltration rate). Cut-off value for prediction of chronic kidney disease was tested using ROC curve, and calculated for sensitivity, specificity.

RESULTS

During the study 284 residents were recruited (177 males and 107 females aged 46 ± 10 years), with body weight 67 ± 13 kg and height 162 ± 9 cm (see Figure 1). Neopterin concentration was normally distributed (K-S Z = 1.175, p = 0.126), with mean 6.66 ± 3.35 ng/ml.

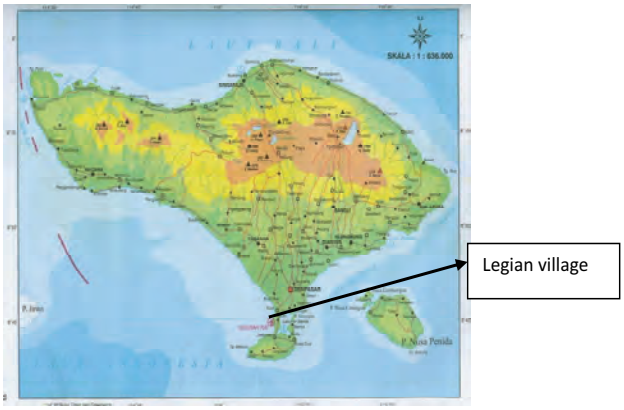

Figure 1. Map of Bali island

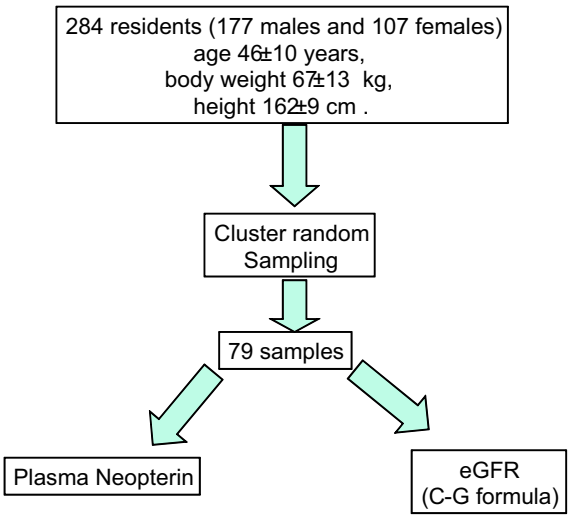

Figure 2. Study profile

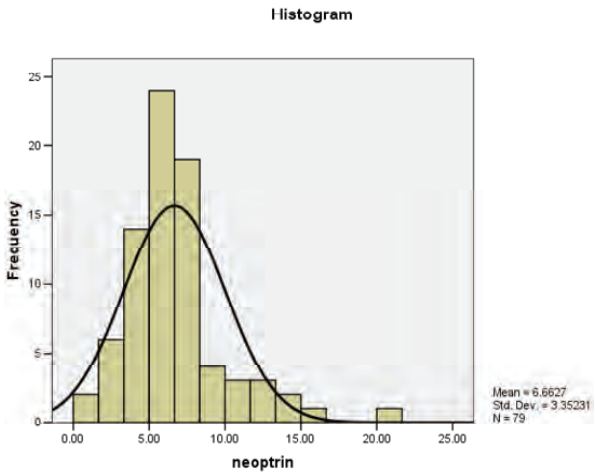

Figure 3. Neopterin concentrations were normally distributed (K-S Z = 1.175, p = 0.126), with mean 6.66 ± 3.35 ng/ml

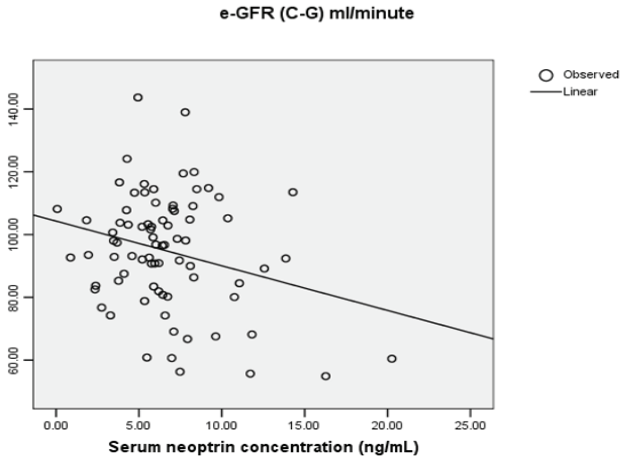

Figure 3. Scattered diagram of the correlation between plasma neoptern concentrations and estimated glomerular filtration rate among individuals in Legian village

There was significant negatively correlation (R = -0.26, RSQ = 0.068, P = 0.021) between plasma neopterin concentrations and estimated glomerular filtration rate calculated by Cockcroft- Gault formula. Using regression equation, it was revealed that every 1 unit increased of plasma neopterin concentrations produce 1.42 ml/minutes decreased of estimated glomerular filtration rate (see Figure 3). In order to determine the cut-off value to predict the presence of chronic kidney disease defined as estimated glomerular filtration rate of less than 60 ml/minutes, receiver characteristic curve was used. It was shown that plasma neopterin concentrations accurately detect chronic kidney disease among samples (area under curve = 0.88; 95%CI 0.74 to 1.00; SE = 0.07; p = 0.02) (see Figure 4).

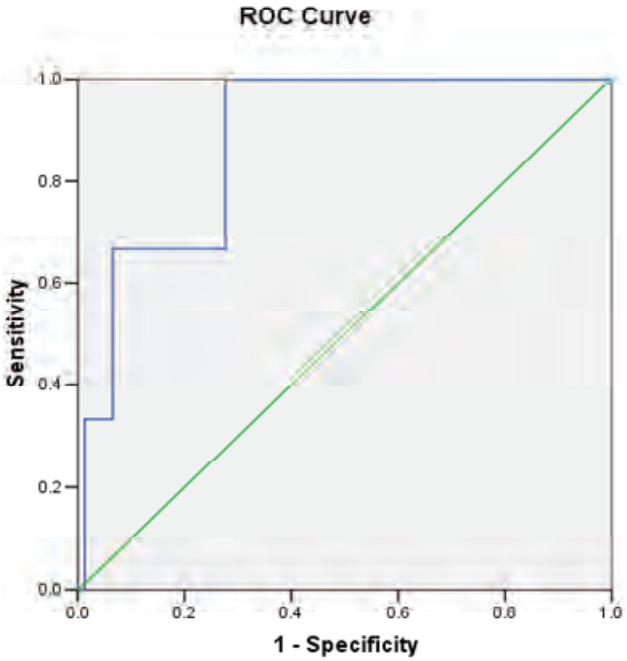

Figure 4. Receiver Operating Characteristic (ROC) curve showing relationship between sensitivity and 1-specificity of particular cut-off value of plasma neopterin concentrations to detect chronic kidney disease and its Area Under Curve (AUC = 0.88; 95%CI 0.74 to 1.00; SE = 0.07; p = 0.02)

Using 7.46 ng/dl as a cut-off value for abnormal plasma beopterin concentrations, it was shown than sensitivity and specificity were 100% and 72% to detect chronic renal failure, consecutively. Using 9.41 ng/dl as cut-off value for abnormal plasma neopterin concentrations, it was shown that sensitivity and specificity were 67% and 87% to detect chronic kidney disease, consecutively.

DISCUSSION

This study showed that there was significant negatively correlation between plasma neopterin concentrations and estimated glomerular filtration rate. Regression equation showed that every one unit increased of plasma neopterin concentrations produce around one and a half ml/minutes decreased of estimated glomerular filtration rate.

Other study has shown that in patients with creatinine clearance 10 – 60 ml/min, creatinine clearance was strongly negative correlated with NP levels. Neopterin also serves as a marker for the progression of diabetic nephropathy.[11]

Neopterin is an independent predictor of all caused and cardiovascular mortality in individuals with and without stable coronary artery disease.[2] Other study also found similar results.[3] It was shown that increased serum neopterin predicts future adverse cardiac events in patients with chronic stable angina pectoris. On the other hand, cardiovascular diseases are major complication for patents with reduced kidney function.

Individuals with CKD are at extremely high cardiovascular risk.[12] More than 50% of deaths in CKD stage 5 cohorts are attributed to cardiovascular disease. The 2-year mortality rate after myocardial infarction in patients with CKD stage 5 is estimated to be 50%.[13] In comparison, the 10-year mortality rate post-infarct for the general population is 25%. Patients with CKD have between a 10- and 20-fold increased risk of cardiac death compared with age-/gender-matched control subjects without CKD.[14-16] Part of this problem may be related to the fact that such individuals are also less likely to receive risk-modifying interventions compared to their non-CKD counterparts.[17]

Less severe forms of CKD also may be associated with significant cardiovascular risk. Evidence for increasing cardiovascular disease morbidity and mortality tracking with mild-to-moderate renal dysfunction (stages 1 to 3) has mainly stemmed from community-based studies.[18-21] These studies documented an inverse relationship between renal function and adverse cardiovascular outcomes (consistently occurring at estimated glomerular filtration rate levels less than 60 ml/min/1.73 m^2). Among high-risk cohorts, baseline creatinine clearance is a significant and independent predictor of short-term outcomes, namely death and myocardial infarction.[15] Adverse cardiovascular outcomes in renal patients are associated with plasma levels of specific biomarkers.[22-24] Troponins, asymmetric dimethylarginine, plasminogen-activator inhibitor type 1, homocysteine, natriuretic peptides, C-reactive protein, serum amyloid A protein, hemoglobin, and ischemia-modified albumin are biomarkers whose levels correlate with cardiovascular outcomes in patients with CKD.[26-27] These observations provide a mechanistic link between chronic inflammation[27], subclinical infections[28], accelerated atherosclerosis, heart-kidney interactions, and negative cardiovascular and renal outcomes.

Our study has determined the cut-off value to predict the presence of chronic kidney disease defined as estimated glomerular filtration rate of less than 60 ml/minutes. It was shown that plasma neopterin concentrations accurately detect chronic kidney disease among general population. Receiver operating characteristic curve showing relationship between sensitivity and 1-specificity of particular cut-off value of plasma neopterin concentrations to detect chronic kidney disease and its area under curve were made. Using 7.46 ng/dl as cut-off value for abnormal plasma beopterin concentrations, it was shown than sensitivity and specificity was 100% and 72% to detect chronic renal failure, consecutively. Using 9.41 ng/dL as cut-off value for abnormal plasma neopterin concentrations, it was shown that sensitivity and specificity were 67% and 87% to detect chronic kidney disease, consecutively. These results may show that neopterin may play a role in bridging the mechanism of cardiorenal syndrome.

Especially, type 4 CRS is characterized by a condition of primary CKD (e.g., chronic glomerular

disease) contributing to decreased cardiac function, ventricular hypertrophy, diastolic dysfunction, and/or increased risk of adverse cardiovascular events.

Macropahages are activated in patients with renal failure, therefore neopterin levels are significant index of both renal function and macrophage activity. Neopterin is produced by monocytes and macrophages in response to stimulation by interferon γ, a cytokine originating mainly from T-helper type-1 lymphocytes and natural killer cells.[6] The amount of neopterin secreted in strongly related to the release of reactive oxygen radicals by cells, reflecting the level of oxidative stress caused by activation of the immune system.[9,10] Oxidative stress will accelerate atherosclerotic process of coronary arteries. This mechanism may play a role in the genesis of atherosclerotic disease and the increased of cardiovascular mortality in chronic kidney disease patients.

CONCLUSION

Neopterin may be used as a novel biomarker for reduced kidney function. It may play a role in the pathogenesis of cardiorenal syndrome in general population.

REFERENCES

1. Consentino F, Patton S, d'Uscio LV. Tetrahydrobiopterin alter superoxyde and nitric oxide release in prehyperetnsive rats. J Clin Invest 1998;101:1530-7.
2. Grammer TB, Fuchs D, Boehm BO, Winkelmann BR, Maerz W. Neopterin as a predictor of total and cardiovascular mortality in individuals undergoing angiography an the Ludwigshaven risk and cardiovascular health study. Clin Chem 2009;55:1135-2246.
3. Valance P, Laone A, Calver A. Accumulation of an endogenous inhibitor of nitric oxide synthesis in chronic renal failure. Lancet 1992;339:572-5.
4. Baigen C, Burbury K, Wheeler D. Premature cardiovascular disease in chronic renal failure. Lancet 2000;356:147-52.
5. US Renal Data System: USRDS. Annual data report. National Health Institute of Health, National Institute of Diabetes and Digestive and Kidney Disease 2002;45:75-86.
6. Arici M, Walls J. End-stage renal disease, atherosclerosis and cardiovascular mortality: is C-rective protein the missing link? Kidney Int 2001;59:407-14.
7. Levine A, Foley RN. Cardiovascular disease in chronic renal insufficiency. Am J Kidney Dis 2000;36:S24-30.
8. Mitch WE, Maroni BJ. Nutritional consideration and indication for dialysis. Am J Kidney Dis 1998;31:185-9.
9. Bengstrom J. Nutrition and mortality in hemodialysis. J Am Soc Nephrol 1995;6: 1329-41.
10. Werener ER, Werner Felmayer G, Watcher H, Mayer B. Biosynthesis of nitric oxide: dependent on pterin metabolism. Rev Physiol Biochem Pharmacol 1996;127:97-123.
11. Yokoyama K, Taji, M, Yoshida H, Nakayama M, Tokutome G, Sakagami H, et al. Plasma pteridine concentrations in patients with chronic renal failure. Nephrol Dial Transplant 2002;17: 1032-6.
12. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. Am J Kidney Dis 1998;32: S112-9.
13. Herzog CA. Dismal long-term survival of dialysis patients after acute myocardial infarction: can we alter the outcome? Nephrol Dial Transplant 2002;17:7-10.
14. Johnson DW, Craven AM, Isbel NM. Modification of cardiovascular risk in hemodialysis patients: an evidence-based review. Hemodial Int 2007;11: 1-14.

15. Logar CM, Herzog CA, Beddhu S. Diagnosis and therapy of coronary artery disease in renal failure, end-stage renal disease, and renal transplant populations. Am J Med Sci 2003;325:214-27.
16. Collins AJ, Li S, Gilbertson DT, Liu J, Chen SC, Herzog CA. Chronic kidney disease and cardiovascular disease in the Medicare population. Kidney Int Suppl 2003;87:S24-31.
17. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004;351:1296-305.
18. Garg AX, Clark WF, Haynes RB, House AA. Moderate renal insufficiency and the risk of cardiovascular mortality: results from the NHANES I. Kidney Int 2002;61:1486-94.
19. Keith DS, Nichols GA, Gullion CM, Brown JB, Smith DH. Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. Arch Intern Med 2004;164:659-63.
20. Sarnak MJ, Coronado BE, Greene T. Cardiovascular diseaserisk factors in chronic renal insufficiency. Clin Nephrol 2002;57: 327-35.
21. Rattazzi M, Puato M, Faggin E, Bertipaglia B, Grego F, Pauletto P. New markers of accelerated atherosclerosis in end-stage renal disease. J Nephrol 2003;16:11-20.
22. Liuzzo G, Biasucci LM, Gallimore JR. The prognostic value of C-reactive protein and serum amyloid a protein in severe unstableangina. N Engl J Med 1994;331:417-24.
23. Panichi V, Maggiore U, Taccola D. Interleukin-6 is a stronger predictor of total and cardiovascular mortality than C-reactive protein in haemodialysis patients. Nephrol Dial Transplant 2004;19: 1154-60.
24. Tonelli M, Wiebe N, Culleton B. Chronic kidney disease and mortality risk: a systematic review. J Am Soc Nephrol 2006;17:2034-47.
25. Urquhart BL, House AA. Assessing plasma total homocysteine in patients with end-stage renal disease. Perit Dial Int 2007;27:476-88.
26. Levin A, Thompson CR, Ethier J. Left ventricular mass index increase in early renal disease: Impact of decline in hemoglobin. Am J Kidney Dis 1999;34:125-34.
27. Schindler R, Beck W, Deppisch R. Short bacterial DNA fragments: Detection in dialysate and induction of cytokines. J Am Soc Nephrol 2004;15:3207-14.
28. Cazzavillan S, Ratanarat R, Segala C. Inflammation and subclinical infection in chronic kidney disease: a molecular approach. Blood Purif 2007;25:69-76.

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