



High Serum Level of Neopterin is a Risk Factor of Patients with Heart Failure

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High Serum Level of Neopterin is a Risk Factor of Patients with Heart Failure

Toshiki Sasaki^a, Yasuchika Takeishi^b, Satoshi Suzuki^a, Takeshi Niizeki^a, Tatsuro Kitahara^a,
Shigehiko Katoh^a, Mitsunori Ishino^a, Tetsuro Shishido^a, Tetsu Watanabe^a, Isao Kubota^a

^aFirst Department of Internal Medicine, Yamagata University School of Medicine, Yamagata, Japan, and ^bDepartment of Cardiology and Hematology, Fukushima Medical University, Fukushima, Japan

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Address for correspondence: Yasuchika Takeishi, M.D., Ph.D.
Department of Cardiology and Hematology
Fukushima Medical University
1 Hikarigaoka, Fukushima 960-1295
Japan
Tel: +81-24-547-1188, Fax: +81-24-548-1821
E-mail: takeishi@fmu.ac.jp

A running head: Neopterin in heart failure

Abstract

Serum neopterin concentration was measured in 198 patients with chronic heart failure (CHF) and 62 control subjects by ELISA. Patients were prospectively followed during a median follow-up period of 745 days with end points of cardiac death or re-hospitalization due to progressive heart failure. Serum concentration of neopterin increased with advancing New York Heart Association (NYHA) functional class ($P < 0.001$). High neopterin group had a significantly higher incidence of cardiac events than low neopterin group ($P < 0.0001$). In the multivariate Cox analysis, serum neopterin concentration was an independent risk factor for cardiac events (hazard ratio 1.70, 95%CI 1.16-2.50, $P = 0.0068$). Serum neopterin concentration is a novel prognostic marker for CHF.

Activated monocytes and macrophages are important cellular sources for circulating proinflammatory cytokines in CHF patients (1). Neopterin is produced by activated monocytes/macrophages upon stimulation with interferon- γ , tumor necrosis factor (TNF)- α and lipopolysaccharides (2). The amounts of neopterin correlate with their capacity to release reactive oxygen species, and neopterin concentrations in body fluids are regarded as an indirect estimate of the degree of oxidative stress emerging during cell-mediated immune responses.

We measured serum concentration of neopterin in 198 patients (116 male and 82 female, mean age 68 ± 13 years) and 62 age-matched control subjects (37 male and 25 female, mean age 66 ± 10 years). Exclusion criteria were acute coronary syndrome, renal insufficiency, malignant diseases, collagen diseases and active systemic inflammatory diseases. Written informed consent was obtained from all patients, and Institutional Review Board on human research approved the study protocol.

There were 46 patients with NYHA functional class I, 81 in class II, 53 in class III, and 18 in class IV. The etiologies of heart failure were identified as dilated cardiomyopathy in 57 (29%), ischemic heart disease in 40 (20%), valvular heart disease in 51 (26%), hypertensive heart disease in 14 (7%), and others in the remaining 36 (18%) patients.

Blood samples were obtained on admission, and serum neopterin concentrations were measured by Neopterin ELISA kit (IBL, Hamburg, Germany) following the manufacture's recommendations. The minimum detectable concentration of neopterin was typically 0.7 nmol/L.

All patients were followed up for median follow-up period of 719 days (range 5 – 1825 days) after discharge. The end points were 1) cardiac death, defined as death from progressive heart failure or sudden cardiac death and 2) re-hospitalization due to progressive heart failure.

Serum neopterin level was increased with advancing NYHA functional class (class I: 5.42 [4.06–6.61], class II: 7.40 [5.52–12.14], and class III & IV: 11.76 [7.58–16.95] nmol/L, $P < 0.0001$). Log (neopterin) was positively correlated with log (BNP) and estimated GFR from the MDRD equation ($R = 0.47$, $P < 0.0001$ and $R = 0.39$, $P < 0.0001$, respectively). Log (neopterin) was negatively correlated with LVEF ($R = -0.23$, $P = 0.002$).

During follow-up periods, there were 55 cardiac events including 13 cardiac deaths and 42 re-hospitalizations for worsening heart failure. From receiver operating characteristic (ROC) curve analysis, we determined the cut off value of serum neopterin levels as 10 nmol/L. Kaplan-Meier analysis clearly demonstrated that high neopterin group had a significantly higher incidence of cardiac events than low neopterin group ($P < 0.0001$ by a log-rank test).

Next, we classified CHF patients into 4 groups according to serum neopterin levels: 1st quartile (< 5.5 nmol/L, $n = 50$), 2nd quartile (5.5-8.1 nmol/L, $n = 50$), 3rd quartile (8.1-12.8 nmol/L, $n = 49$), and 4th quartile (> 12.8 nmol/L, $n = 49$). The relative risk of cardiac events was 2.6-fold in the 3rd quartile and 11.1-fold in the 4th quartile ($P < 0.001$) compared to the 1st quartile.

To determine risk factors for cardiac events, the Cox proportional hazard regression analysis was used. Variables with a P value less than 0.05 in the univariate analysis were

entered into the multivariate Cox analysis. Levels of sodium, log (BNP) and log (neopterin) were independent predictors for cardiac events in patients with CHF [sodium: HR 0.73, 95%CI 0.55–0.98, P = 0.0362; log (BNP): HR 1.89, 95%CI 1.14–3.12, P = 0.0133; log (neopterin): HR 1.70, 95%CI 1.16–2.50, P = 0.0068].

Although neopterin increases in many clinical states including acute coronary syndrome and CHF (2-4), prognostic value of serum neopterin level has not been previously examined in CHF. In the present study, we demonstrated that high serum neopterin level was associated with high cardiac events rates, and neopterin was an independent prognostic factor of future cardiac events by the multivariate Cox proportional hazard analysis. These data suggest that serum neopterin is useful for risk stratification of patients with CHF.

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The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology. (4)

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