Hindawi Publishing Corporation
Mediators of Inflammation
Volume 2012, Article ID 476979, 6 pages
doi:10.1155/2012/476979

Research Article

Association between Serum Neopterin and Inflammatory Activation in Chronic Kidney Disease

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Received 14 June 2012; Revised 11 July 2012; Accepted 11 July 2012

Academic Editor: Giamila Fantuzzi

Background. The serum levels of neopterin, a marker associated with cell-mediated immunity are elevated in chronic kidney disease (CKD). We evaluated serum neopterin levels and investigated its association with markers of inflammation in a cross-section of CKD subjects without known cardiovascular disease. *Methods.* Serum neopterin levels were measured in 118 patients with stage 3–5 CKD and 41 healthy subjects with normal kidney function (HC). Patients with known cardiovascular disease were excluded. We also estimated highly sensitive CRP (hsCRP) and interluekin-6 (IL-6), tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ) in the CKD subjects. All assays were done using commercially available ELISA kits. The correlation between neopterin and markers of inflammation were investigated. *Results.* Of the CKD population, 82 were in stage 5 (60 stage 5 D), 24 in stage 4, and 12 in stage 3. The mean age was 51.04 ± 1.3 years and 66% were males. The commonest cause of CKD was diabetes (36%). Serum neopterin levels were 5-fold higher in CKD patients as compared to HC (74.8 ± 3.6 versus 15.0 ± 2.8 nmol/L, $P < 0.0001$). There was a graded increase of serum neopterin from stages 3 to 4 and 5. CKD 5 D patients exhibited significantly higher levels compared to nondialysis stage 5 patients ($P < 0.0001$). An inverse correlation was noted between serum neopterin and eGFR ($r = -0.359$, $P < 0.0001$). Serum neopterin correlated with hsCRP ($r = 0.285$, $P = 0.002$), IL-6 ($r = 0.212$, $P = 0.034$), and IFN-γ ($r = 0.32$, $P = 0.001$) but not with TNF-α. *Conclusion.* Serum neopterin level is elevated and correlates with the severity of CKD. The elevation correlates with elevation of most, but not all, inflammatory markers. Its role in future development of cardiovascular disease and modulation with anti-inflammatory therapies needs further studies.

1. Introduction

Neopterin, a pyrazino-pyrimidine compound, is synthesized by monocytes and macrophages in response to interferon-(IFN-) γ produced by activated T cells. Neopterin levels are elevated in conditions of T-cell or macrophages activation [1]. It enhances macrophage cytotoxicity through its interactions with reactive oxygen, nitrogen, and chloride species [2].

Neopterin is a marker of cellular immune response [3]. Its levels are elevated in several conditions including autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis [4]; infections such as hepatitis, human immunodeficiency virus, and cytomegalovirus [5–7]; cancers like hepatocellular, gastric, and urothelial carcinomas [8, 9]; congestive heart failure; coronary artery disease and myocardial infarction and transplant rejection [10–13]. Neopterin has been reported as a marker of disease progression and complication in diabetes [14].

Recent studies have shown a strong association of neopterin with CVD [15, 16]. Sasaki et al. [17] showed association of high levels with increased cardiac events rates. In a cross-sectional study, neopterin levels correlated with the extent of atherosclerosis, especially coronary and peripheral vascular disease [18]. In epidemiological studies, neopterin levels can distinguish patients with unstable angina from stable angina [12, 13]. Neopterin has been identified as a potential risk factor for cardiovascular disease in dialysis patients [19].

Chronic kidney disease (CKD) subjects are at a high risk of developing CVD. The CVD risk goes up with declining

Table 1: Characteristic of CKD study subjects.

	CKD nondialysis	CKD-Dialysis	HC
Number of cases	60	58	41
Age (yrs)	51.5 ± 1.5	52.0 ± 1.7	46.8 ± 2.2
Gender M/F	40/20	44/14	31/10
Body mass index (kg/m^2)	22.8 ± 0.5		22.7 ± 0.3
Systolic blood pressure (mm Hg)	142.1 ± 2.3	137.9 ± 2.4	110.3 ± 2.0
Diastolic blood pressure (mm Hg)	85.2 ± 1.2	85.0 ± 1.2	80.6 ± 1.4
Diabetes	18 (30%)	22 (38%)	—
Hypertension	50 (83%)	48 (83%)	—
Current smokers	16 (27%)	15 (26%)	5 (12%)
Hemoglobin (mg/dL)	10.31 ± 0.3	9.7 ± 0.3	13.6 ± 0.6
eGFR ($mL/min/1.73\,m^2$)	17.0 ± 1.3	8.7 ± 1.0	106.8 ± 4.2
Total cholesterol (mg/dL)	165.9 ± 8.1	156.6 ± 6.4	
LDL cholesterol (mg/dL)	95.1 ± 8.9	88.1 ± 4.8	
Calcium (mg/dL)	7.9 ± 0.2	8.2 ± 0.2	
Inorganic phosphate (mg/dL)	6.1 ± 0.2	6.4 ± 0.3	

GFR and dialysis patients have a 35-fold greater CVD mortality risk [20]. High prevalence of chronic inflammation and its link to CVD, especially progressive atherosclerotic disease in CKD [21–23] have fuelled interest in understanding the extent and mechanism of this association. Elevated levels of CRP and pro-inflammatory cytokines such as interleukin- (IL-) 6 and tumor necrosis factor- (TNF-) α have been demonstrated to be associated with increased cardiovascular mortality in dialysis patients [24, 25]. This has led to inflammatory activation being dubbed as a nontraditional CVD risk factor in CKD. The exact understanding of how inflammation causes CVD, however, remains unclear.

Serum and urine neopterin levels are elevated in patients with kidney diseases [26–28]. The association between inflammatory activation and neopterin has not been examined in CKD. We and others have recently shown a link between inflammation and abnormalities in T-cell subpopulation in CKD subjects [29, 30]. It is possible that these activated T-cells could mediate CVD through neopterin. We hypothesized that serum neopterin will be significantly elevated in CKD subjects and show association with other markers of inflammation.

2. Materials and Methods

2.1. Study Population. Over a 6-month period (July–December 2011), 118 patients with stage 3–5 CKD were recruited in this cross-sectional study from the outpatient clinic and ward population of nephrology department, Postgraduate Institute of Medical Education and Research, Chandigarh, a large multispecialty hospital in north India. Patients over the age of 70, those with known coronary artery disease, heart failure, malignancies, active infections and taking drugs that can modulate inflammatory response were excluded. Out of these, 58 subjects were on hemodialysis (HD) and 60 were stage 3–5 predialysis CKD subjects. Estimated glomerular filtration rate (eGFR) was calculated using MDRD formula [31], and CKD stages were defined according to KDOQI criteria [32]. Detailed history was taken and all subjects underwent a thorough clinical examination. Details of clinical features and laboratory investigations were recorded. Hypertension and diabetes were diagnosed according to the standard clinical criteria. Smoking status was categorized as current smoker and nonsmoking as never smoking and stopped smoking. As part of workup for CKD, patients were screened for evidence of CV disease, infections (including tuberculosis), and malignancies using standard tools including chest skiagram, abdominal ultrasound examination and upper GI endoscopy. All patients underwent 12-lead electrocardiogram and echocardiography. Other tests, such as stress thallium or coronary angiography were done if indicated. To evaluate the normal range of neopterin, we recruited 41 healthy volunteers from amongst the institute staff and patient's relatives with normal kidney function as judged by medical history, physical examination, urinalysis, and serum creatinine estimation. All subjects gave informed consent, and the Institution Ethics Committee approved the study.

2.2. Estimation of Inflammatory Markers and Neopterin Levels. After recruitment, subjects were asked to report in a fasting state. Blood samples were collected in a vacutainer, serum was separated and stored in cryovials at -80°C until analysis. Commercially available enzyme-linked immunosorbent assays kits were used to measure serum IL-6 and TNF-α, IFN-γ (BD Biosciences, San Jones, CA), hsCRP (Diagnostics Biochem Canada Inc., London, Ontario, Canada), and neopterin (DRG International Inc, Mountainside, NJ, USA). All the samples were analyzed in duplicate. These markers were selected because of their documented association with CV complication in CKD and their association with serum neopterin level in other diseases.

2.3. Statistics. Data were expressed as mean ± standard error of mean (SEM) when distributed normally, or as median (interquartile range). Statistical Package for Social Sciences (SPSS) v 16.0 was used to analyze the data. Mann-Whitney U test, independent t test, and Pearson and Spearman correlation tests were performed as appropriate. All P values were calculated two-sided, and a value of <0.05 was considered significant.

3. Results

Detailed characteristics of study subjects are shown in Table 1. Most of the CKD patients were males, 85% had hypertension, 34% had diabetes, and 26% were current smokers. There was no difference in age and gender distribution

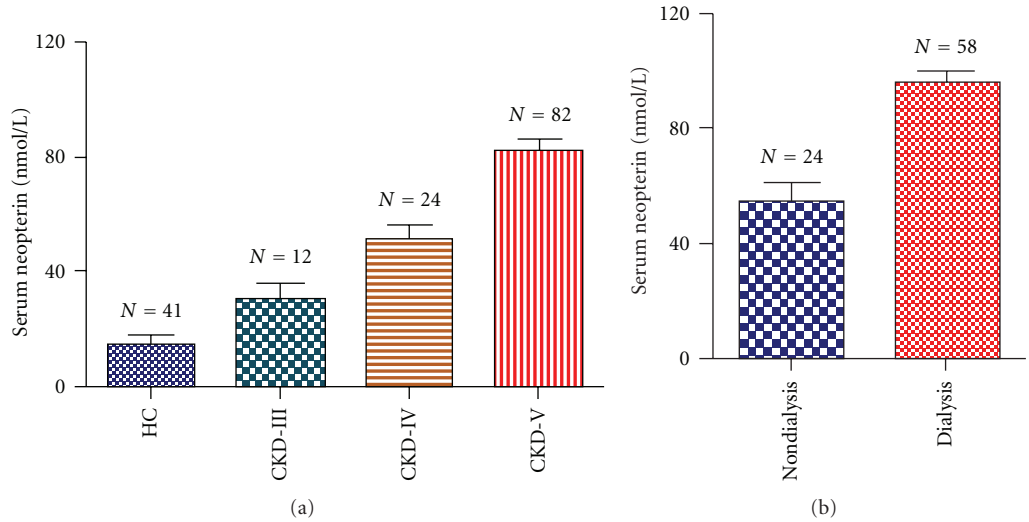

Figure 1: Showing (a) Serum neopterin levels in healthy subjects (HC) and in those with different stages of chronic kidney disease (CKD). P value are as follows: HC versus CKD III, 0.001; HC versus CKD IV, <0.0001; HC versus CKD V, 0.0001; CKD III versus CKD IV, 0.01; CKD III versus CKD V, 0.01 and CKD IV versus CKD V, 0.01, and (b) serum neopterin level in dialysis patients as compared to those nondialysis CKD patients ($P < 0.001$).

between CKD and non-CKD subjects. Of the 118 CKD patients, 82 were in stage 5, 24 in stage 4, and 12 in stage 3. A total of 58 patients were on dialysis for 22.6 ± 3.0 months.

Compared to healthy subjects, serum neopterin level was approximately 5-fold higher in CKD patients (74.8 ± 3.6 versus 15.0 ± 2.8 nmol/L, $P < 0.0001$). There was no effect of diabetes, hypertension, smoking, age, or gender on the levels. A graded increase was noted in neopterin level from CKD stage 3 to 5 (29.9 ± 4.1, 51.2 ± 6, and 82.4 ± 4.2 nmol/L, $P < 0.001$, Figure 1(a)). The serum hsCRP levels were 95.7 ± 5.4 μg/mL, IL-6 17.3 ± 2.6 pg/mL, TNF-α 7.9 ± 1.0 pg/mL, and IFN-γ8.3 ± 0.9 pg/mL in the CKD population.

The serum neopterin levels exhibited a significant inverse correlation with eGFR ($r = -0.359$, $P < 0.0001$), and had positive associations with hsCRP ($r = 0.285$, $P = 0.002$), IL-6 ($r = 0.212$, $P = 0.03$), and IFN-γ ($r = 0.32$, $P = 0.001$) in the CKD subjects (Figure 2). We did not find a significant correlation between neopterin and TNF-α.

We further subdivided stage 5 CKD patients to dialysis and nondialysis groups. Neopterin level was significantly higher in dialysis group as compared to non-dialysis group (98.8 ± 4.2 versus 58.4 ± 6.7 nmol/L, $P < 0.0001$, Figure 1(b)). There was no correlation between duration of dialysis and neopterin levels, however. The hsCRP (115.1 ± 7.3 versus 68.9 ± 11.91 μg/mL, $P = 0.002$) and IFN-γ (10.9 ± 1.6 versus 7.0 ± 1.3 pg/mL, $P = 0.04$) were also significantly higher in dialysis group. The IL-6 level was also increased in dialysis patients but difference was not significant (19.9 ± 4.0 versus 12.1 ± 3.0 pg/mL, $P = 0.1$). No difference was noted in TNF-α level.

4. Discussion

The present study shows that CKD patients exhibit a significant increase in serum neopterin levels compared to healthy subjects, and this increase is correlated with increased circulating levels of several markers of inflammation (hsCRP, IL-6, and IFN-γ). We did not note any correlation between serum neopterin and TNF-α levels. Neopterin levels show continuous rise with falling GFR, and are further increased in dialysis patients. The finding of inverse association of renal function with serum neopterin and a stepwise increase in serum neopterin with increasing stages of CKD is consistent with previous reports [27, 33] and suggest that impaired renal elimination and/or increased generation, or an adverse effect of inflammation on renal function might be responsible for this progressive increase.

CKD subjects showed evidence of inflammatory activation at all stages. The CRP, IL-6, IFN-γ, and TNF-α values in the CKD subjects are significantly higher than those previously reported by us in non-CKD subjects [29, 30, 34]. A heightened state of inflammation is a consistent feature of CKD, as reflected by elevated levels of IL-6 [35], IL-18 [36], leukocytes [37], fibrinogen [38], hyaluronan [39], CRP [40], and pentraxin-3 (PTX3) [41]. IL-6 is produced by activated monocytes and macrophages, activated T and B cells, and endothelial cells. In turn, IL-6 induces the release of acute phase reactants from the liver [42]. C-reactive protein is one of the major acute phase reactants, and probably acts in host defense in a manner similar to immunoglobulins [43]. Moreover, inflammatory activation has consistently been associated with CV morbidity and mortality in CKD [21–23]. Attempts to find a link between inflammation and CV disease are ongoing, but are far from conclusive.

The positive association of serum neopterin level with hsCRP, IL-6, and IFN-γ in CKD suggests a link with the overall state of inflammation. Our study also demonstrated a twofold increase in neopterin levels in dialysis patients as compared to those not on dialysis, but with comparable GFR. This suggests that dialysis might further increase

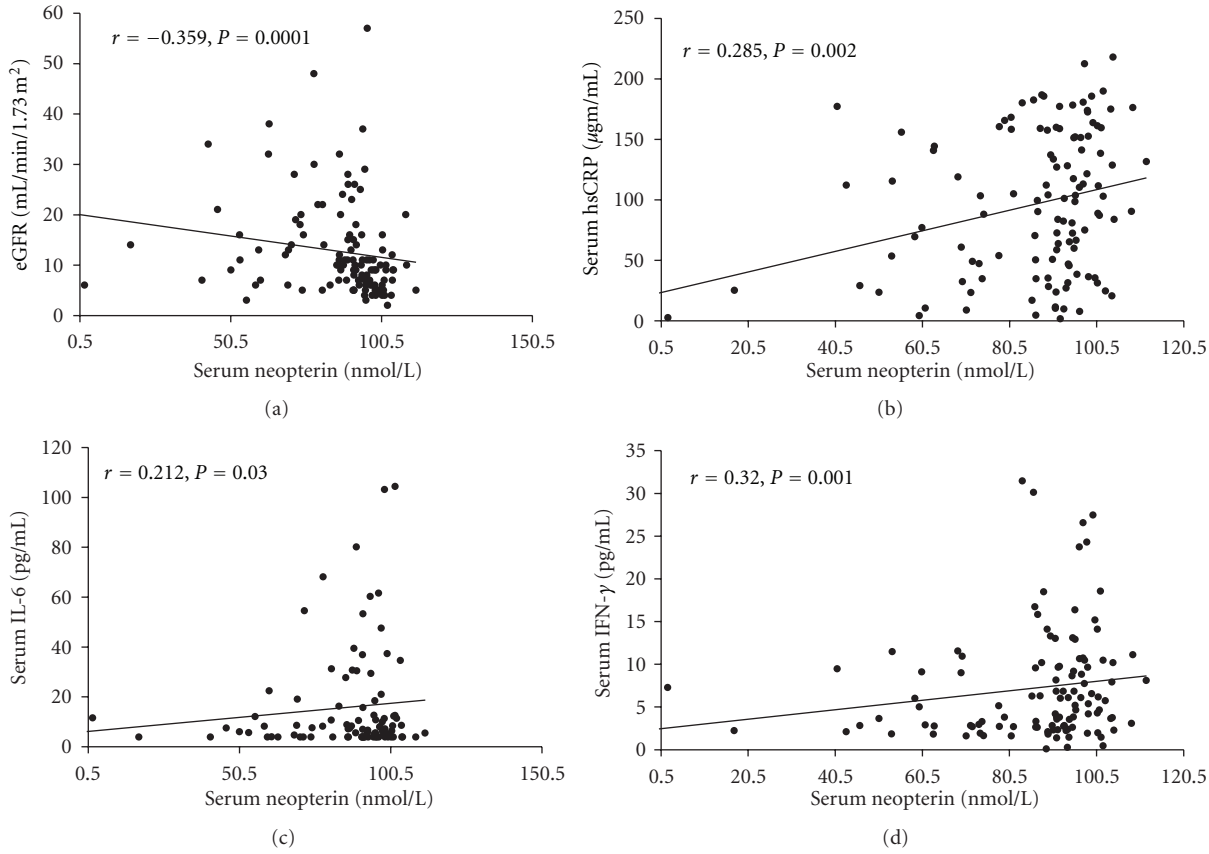

Figure 2: Scatter plot showing correlation of serum neopterin with (a) eGFR, (b) serum hsCRP, (c) IL-6 and (d) IFN-γ in CKD subjects.

the production of neopterin. These subjects also showed higher levels of inflammatory markers, probably as a result of inflammatory activation and cytokine generation by activated leukocytes as a result of interaction between blood and dialysis membranes [44] which then leads to increased neopterin synthesis and/or release.

The finding of increased neopterin levels in CKD could have clinical significance. Neopterin can predict morbidity and mortality in chronic inflammatory and infectious diseases [45]. Serum neopterin was related to the anemia, weight loss, and cachexia in malignant tumors and chronic diseases (Murr G International Eurogin-east conference, Vilnius, Sept, 2001). Neopterin has been suggested as a marker of plaque progression and instability in patients with coronary artery disease [46, 47]. In a study on 2380 patients with stable angina, neopterin levels predicted future major CV events [48]. CKD is a well-known risk factor for cardiovascular disease, and it is possible that part of this increased risk could be mediated through neopterin. The adverse effects of neopterin can be due to its effect on intracellular redox state, leading to activation of constitutive and inducible NO synthase [49, 50]. Neopterin is biologically stable, and could be used as diagnostic or prognostic marker.

Our study had some limitations. This is a cross-sectional study, and measurements have been done at a single time point. Most of our patients had newly diagnosed CKD. Whether the relationship still holds in patients on long-term dialysis is not certain. Also, whether these findings are valid for patients from other geographic areas and/or ethnic backgrounds needs to be confirmed. Our patients did not have overt CV disease but still showed rise in neopterin levels. It would be interesting to follow up these patients to see if increased levels predict future development of vascular disease. If this association is confirmed, a role could be suggested for therapies that could modulate inflammatory activation and/or target neopterin.

In summary, CKD patients exhibit elevated levels of serum monocyte activation marker neopterin. The degree of elevation correlates with the stage of kidney disease and inflammatory activation. This association needs to be confirmed in larger studies, and the link between inflammatory activation and elevation in serum neopterin levels and their contribution to the clinical events, especially CVD, requires further studies.

Conflict of Interests

The authors declared that there is no conflict of interests.

Authors' Contributions

AKY: collected samples, performed experiments, analyzed the data and wrote the manuscript. VS: collected samples,

performed laboratory experiments, and analyzed the data. VJ: Designed the study, supervised the project, helped with data analysis and wrote the manuscript. All authors read and approved the manuscript.

Acknowledgment

The authors acknowledge the grant support of the Indian Council of Medical Research.

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