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RESEARCH ARTICLE

Usefulness of serum neopterin levels in acute decompensated heart failure to predict renal dysfunction

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Abstract

Context: Neopterin serum concentration increases in the presence of renal dysfunction.

Objective: We sought to determine the relationship between admission serum neopterin levels and worsening renal function (WRF) in patients with heart failure (HF).

Methods: We prospectively measured serum neopterin levels in patients with HF and the patients were subdivided into two groups: with and without WRF during hospital admission.

Results: Logistic regression analysis showed that high serum neopterin levels at admission were associated with a greater likelihood of developing WRF.

Conclusions: Patients admitted to hospital with HF, elevated serum neopterin levels are associated with an increased risk of developing WRF.

Keywords: Renal function, acute heart failure, neopterin, inflammation

Introduction

Renal dysfunction is a common finding in patients with heart failure, and an independent predictor of impaired clinical outcomes in these patients. In large registries of patients hospitalized for acute decompensated heart failure (ADHF), around 30% of patients have moderate or severe renal dysfunction, and this figure can exceed 50% when mild renal dysfunction is included in the estimation (McAlister et al., 2004; Smilde et al., 2004). Studies in ADHF patients showed that worsening of renal function (WRF) lengthens hospital stay and, in some studies, it is associated with increased mortality and recurrent hospitalization during follow-up (Cowie et al., 2006; Metra et al., 2008). The causes underlying WRF are multifactorial, but they do, to some extent, relate to derangements in cardiorenal interactions that result from intensive diuretic treatment in patients with congestive heart failure. The detection of WRF is usually based on serial measurements of serum creatinine levels, but this marker appears to increase rather late in the process of end-organ dysfunction. Identifying preexistent renal dysfunction or renal injury leading to impaired kidney early during admission may prevent the development of advanced or irreversible WRF (Forman et al., 2004; Metra et al., 2008).

Neopterin, a pyrazino-pyrimidine compound, is an intermediate product of biopterin, a nerve transmitter coenzyme. It is, synthesized by monocytes and macrophages as result of interferon γ production by activated T cells. Neopterin levels are elevated in a variety of diseases in which T cells or macrophages are activated (Huber et al., 1984). Neopterin enhances macrophage cytotoxicity through its interactions with reactive oxygen, nitrogen, and chloride species (Hoffmann et al., 2003). Neopterin levels are also increased in the serum and urine in patients with

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nephrotic syndrome, chronic and acute glomerulonephritis, and in those with chronic renal failure (Godai et al., 1991; Oda et al., 1999). The present study sought to determine the relationship between admission serum neopterin levels and WRF in patients admitted to hospital with ADHF.

Material and methods

Patients

We prospectively enrolled 153 consecutive patients admitted into a tertiary care hospital with a diagnosis of ADHF. Patients were classified according to the categories established in the diagnosis and treatment guidelines of the European Society of Cardiology (type I, ADHF, *de novo* or as decompensation of chronic heart failure; type II acute hypertensive heart failure; type III, acute pulmonary edema; type IV, cardiogenic shock; type V, high-output failure; and type VI, predominantly right heart failure) (Gheorghiade et al., 2005; Nieminen et al., 2005). All patients gave informed written consent to take part in the study, which was approved by the institutional Ethics Committee. We did not include patients with severe primary valve heart disease ($n=11$), myocarditis ($n=2$), cardiac tamponade ($n=3$), aortic dissection ($n=1$), pulmonary embolism ($n=4$), high output syndrome ($n=3$), or requiring dialysis or ultrafiltration ($n=9$). Patients who had undergone organ transplantation or were receiving immunosuppressive therapy ($n=5$), had multiorgan failure or sepsis ($n=12$), and those undergoing interventional procedures able to cause a rise in serum creatinine during the hospitalization ($n=7$) were also excluded. Hence, 96 patients were included in the study.

All patients underwent clinical and laboratory characterization at the time of hospital admission (Table 1).

Table 1. General characteristics of patients admitted to hospital with ADHF who developed WRF and those who did not.

	WRF ($n=31$)	No WRF ($n=65$)	p
Age–years	61 ± 12	66 ± 11	0.04
Male gender, *n* (%)	28 (90)	49 (75)	0.08
Cardiovascular risk factor			
Diabetes mellitus, n (%)	13 (42)	18 (28)	0.16
Dyslipidaemia, n (%)	9 (29)	38 (59)	0.007
Current smokers, n (%)	12 (39)	27 (41)	0.79
Hypertension, n (%)	18 (58)	33 (51)	0.50
GFR, mL/min/1.73 m^2	61.6 ± 8	70.5 ± 13.9	0.001
Serum creatinine (mg/dL)	0.99 ± 0.25	0.95 ± 0.21	0.44
LVEF (%)	47 ± 9	45 ± 10	0.23
Classification of heart failure			0.71
Type I	7 (23)	21 (32)	
Type II	10 (32)	18 (28)	
Type III	6 (19)	15 (23)	
Type IV	6 (19)	7 (11)	
Type VI	2 (6)	4 (6)	
Medication before hospitalization			
Digoxin, *n* (%)	2 (6)	3 (5)	0.70
Aldosterone antagonists, *n* (%)	7 (23)	12 (18)	0.63
ACEi and/or ARBs, *n* (%)	12 (39)	20 (31)	0.44
Furosemide, *n* (%)	29 (93)	64 (98)	0.48
Beta-blockers, *n* (%)	25 (81)	59 (91)	0.16
Thiazides, *n* (%)	2 (6)	3 (5)	0.70
Statins, *n* (%)	25 (81)	59 (91)	0.16
Medication received during hospitalization			
Intravenous furosemide (mg)	487 ± 100	451 ± 58	0.02
Intravenous inotropic agents, *n* (%)	10 (33)	13 (20)	0.07
Intravenous vasodilators, *n* (%)	11 (36)	19 (30)	0.70
ACEi and/or ARBs, *n* (%)	19 (61)	52 (80)	0.03
Aldosterone antagonists, *n* (%)	7 (22)	25 (38)	0.04
Thiazides, *n* (%)	3 (11)	8 (13)	0.90
Biochemistry findings			
C-reactive protein (mg/L)	5.70 (4–6.70)	5.10 (4–6.90)	0.09
Brain natriuretic peptide (pg/mL)	470 (210–660)	452 (298–661)	0.19
Neopterin (nmol/L)	6.89 (2.61–9.83)	5.03 (2.74–9.06)	<0.001

Note: Data are expressed as mean ± standard deviation or *n* (%) for categorial variables or median (interquartile range).
ACEi, angiotensin converting enzyme inhibitors; ADHF, acute decompensated heart failure; ARBs, Angiotensin II receptor blockers; GFR, glomerular filtration rate; LVEF, left ventricular ejection fraction; WRF, worsening renal function.

At least one Doppler-echocardiography exam was performed in all patients 1–3 days before discharge. In patients receiving furosemide treatment we recorded (i) the daily dose received by the patient prior to hospital admission; (ii) the total dose administered intravenously during the first day of hospitalization; and (iii) the daily dose administered to the patient at the time of hospital discharge. The use of thiazide diuretics, dopamine and inotropic drugs (namely dobutamine or levosimendan), was left to the discretion of the managing physician. In general, thiazide diuretics were added when insufficient diuresis was obtained with furosemide alone. Inotropic agents were used in accordance with ESC guidelines. The dose of dopamine (i.v. infusion) used in this setting did not exceed 3 μg/kg/min. For the diagnosis of WRF 2 criteria were required: >0.3 mg/dL increase in serum creatinine concentration and >25% creatinine increase from admission (Gottlieb et al., 2002; Cowie et al., 2006; Metra et al., 2008). The time in which increased serum creatinine concentration was at fifth day after hospital admission.

Blood samples

Serial blood samples were obtained in every patient on days 1, 3, 5 and at hospital discharge, for the assessment of creatinine and glomerular filtration rate (GFR). Neopterin assessment was carried out from 08.00 AM to 3 PM to avoid the diurnal variation of neopterin levels, as reported by our group (Garcia-Gonzalez et al., 2008; Dominguez-Rodriguez et al., 2009). Estimated GFR was calculated using the standard 4-variable Modification of Diet in Renal Disease (MDRD) equation. This is currently the best clinical method for the indirect assessment of renal function in heart failure patient (O'M Levey et al., 1999). Serum neopterin concentrations were measured using a commercially available immunoassay (ELISA Kit, DRG Instruments, Marburg, Germany). The lowest detection limit for neopterin was 0.7 nmol/L and the intraassay and interassay coefficients of variability were 5.3% and 9%, respectively. Brain natriuretic peptide (BNP) was measured using a high-sensitivity, quantitative sandwich enzyme immunoassay (ALPCO, Salem, New Hampshire, USA). In this assay, the lowest detection limit of BNP is 11.6 pg/mL. Coefficients of variation were 4.1 % and 5.1 % for intra and interassay variability, respectively. Concentrations of serum C-reactive protein (CRP) were measured by an ultrasensitive enzyme-linked immunosorbent assay kit (DRG Instruments GmbH). In this enzyme-linked immunosorbent assay, the lowest detection limit of CRP was 0.010 mg/L. Coefficients of variation were 5.12% and 11.6% for intra and interassay variabilities, respectively.

Statistical analysis

Results for normally distributed continuous variables are expressed as mean ± SD; continuous variables with non-normal distribution are presented as median values and interquartile intervals; categorical data are expressed as percentages. Analysis of normality of the continuous variables was performed with the Kolmogorov-Smirnov test. Differences between groups were assessed by unpaired two-tailed t test and the Mann-Whitney U test for continuous variables, as appropriate. Categorical data and proportions were analyzed by use of χ^2 or Fisher's exact test when required. Neopterin levels had a nonnormal distribution and were therefore logarithmically transformed before regression analysis to fulfill the conditions required for this type of analysis. A multivariate binary logistic regression analysis was performed to assess predictors associated with WRF, including as independent variable neopterin and using a stepwise selection method. We included these variables with possible effects on the WRF, such as age, gender, GFR, left ventricular ejection fraction, use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, antialdosterone agents, and use of intravenous furosemide dose (Metra et al., 2008). Correlation between neopterin and GFR was assessed with the two-tailed Pearson's rho. The optimal cut-off point for neopterin to predict WRF was calculated with receiving operating characteristics (ROC) analysis. Data were analyzed using SPSS version 15.0 (SPSS, Inc., Chicago, Illinois). A p value <0.05 was considered statistically significant. All tests were two sided.

Results

Thirty-one patients (32%) developed WRF. The characteristics of the patients with and without WRF are shown in Table 1. The etiology of heart failure in our study was as follows: 30% ischemic, 50% nonischemic and 20% hypertensive. Patients in the group with WRF were younger than patients in the group without WRF. There were no significant differences between groups regarding pre-admission treatment, clinical presentation (European Society of Cardiology guidelines) at admission and presence of conventional coronary risk factors for coronary artery disease, with the exception of dyslipidaemia, which were lower in the group with WRF. Renal function at admission, as assessed by GFR, was significantly reduced in the group with WRF. During hospitalization, all patients received intravenous furosemide but the total dose administered was significantly higher in those who developed WRF. Twenty four percent of patients received treatment with intravenous inotropic drugs, with a non-significant trend to higher use in the group with WRF (Table 1). Patients without WRF had a higher usage of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and antialdosterone agents. In comparison to patients who did not develop WRF, those with WRF had significantly higher serum neopterin levels (Table 1 and Figure 1). We carried out partial multivariable binary logistic regression analysis, using a stepwise selection model. This analysis showed that neopterin was a significant predictor of WRF (OR ranging from [1.687, CI 95% 1.192–2.387, $p = 0.003$] to [1.853, CI 95% 1.338–2.566, $p < 0.001$]; Table 2).

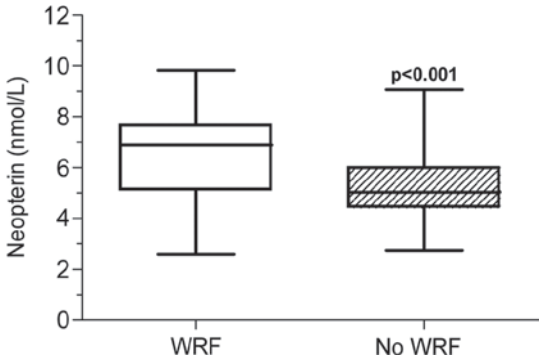

Figure 1. Boxplot showing differences in neopterin levels between patients with and without worsening renal function (WRF).

Table 2. Multivariate binary logistic regression analysis including neopterin as the main independent variable.

	OR	95% Confidence interval	*p*
Model 1 (unadjusted)			
Neopterin	1.687	1.192–2.387	0.003
Model 2			
Neopterin	1.742	1.253–2.421	0.001
LVEF	1.029	0.975–1.085	0.298
GFR	0.95	0.905–1.002	0.08
Model 3			
Neopterin	1.722	1.238–2.396	0.001
CRP	1.496	0.808–2.771	0.20
GFR	0.948	0.904–1.005	0.18
Model 4			
Neopterin	1.836	1.329–2.536	<0.001
ACEi and/or ARBs	1.076	0.396–2.921	0.88
Model 5			
Neopterin	1.840	1.335–2.537	<0.001
Aldosterone antagonists	1.113	0.137–9.042	0.92
Model 6			
Neopterin	1.853	1.338-2.566	<0.001
I.V. furosemide dose >100 mg/day	0.870	0.251-3.020	0.82

Note: ACEi, angiotensin converting enzyme inhibitors; ARBs, Angiotensin II receptor blockers; CRP, C-reactive protein; LVEF, left ventricular ejection fraction; GFR, glomerular filtration rate.

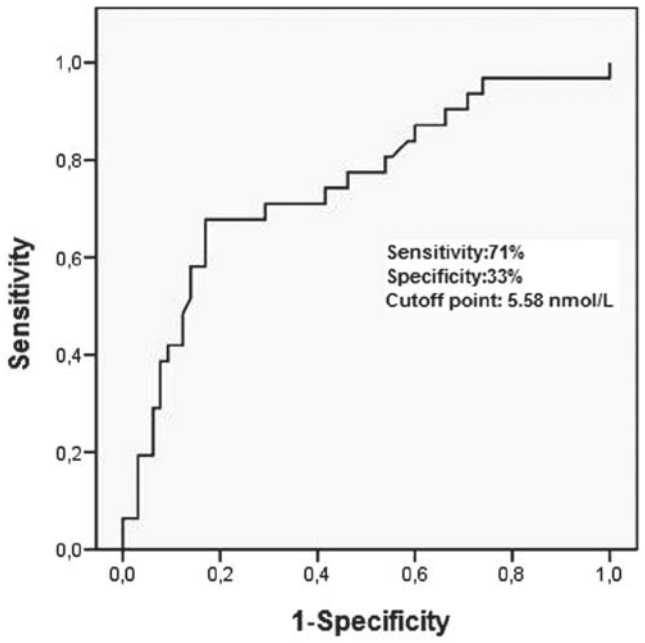

Figure 2. ROC analysis shows the power of neopterin levels to predict worsening renal function (WRF). The area under the curve was 0.74 (CI 95% 0.64–0.85, $p < 0.001$).

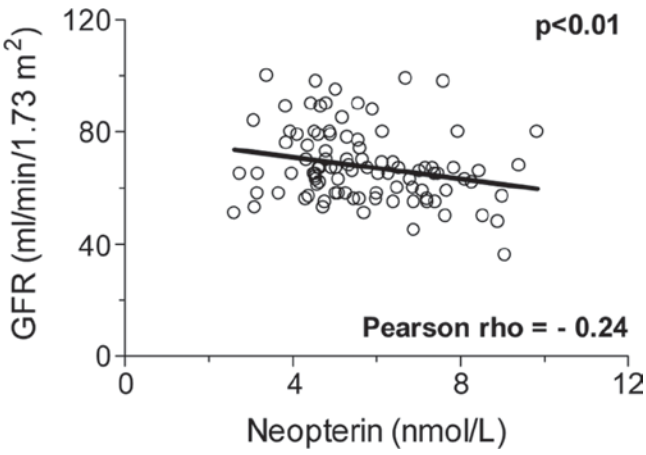

Figure 3. Correlation between neopterin levels and glomerular filtration rate (GFR) in the patients included in the study (Pearson rho = –0.24; $p = 0.01$).

Neopterin levels were a good predictor of WRF with an area under the receiver operating characteristic curve of 0.74 (CI 95% 0.64–0.85, $p < 0.001$). An optimized cutoff point of 5.58 nmol/L was identified, which showed 71% sensitivity and 33% specificity (Figure 2). Additionally, serum neopterin levels showed a significant inverse correlation with GFR (Pearson rho = –0.24; $p = 0.01$; Figure 3).

Discussion

The main and original finding of our study in patients with ADHF is that neopterin levels, as assessed at hospital admission, were a predictor of the development of WRF, in turn a marker of impaired patient outcome. Renal failure is often associated with heart failure and adversely affects clinical outcomes (Akhter et al., 2004; McAlister et al., 2004). In the present study, neopterin, a marker of macrophage activation, was a better predictor of WRF than variables such as GFR, left ventricular ejection fraction and treatment with furosemide (Metra et al., 2008). This finding suggests that enhanced activation of the monocyte-macrophage system may be a marker of risk for WRF and/or a pathogenic mechanism in the development of WRF in patients with ADHF.

Studies have shown that WRF is associated with the intensive use of diuretics (Metra et al., 2008). Other studies, however, have failed to show a causal relation between loop diuretic use and the development of WRF (Belziti et al., 2010). In the present study, the group with WRF was more likely to receive treatment with loop diuretics, but

the association lost statistical significance on multivariate analysis. Compared to patients without WRF, subjects in the WRF group were less likely to receive treatment with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and antialdosterone agents during hospitalization, probably because of their more severe renal deterioration and because WRF limited their use.

The role of monocyte-macrophages in the progression of heart failure is incompletely understood at present. It has been suggested that macrophage activation could represent an attempt to repair tissue damage or a physiological response to cardiac dysfunction (Apostolakis et al., 2010). Increased neopterin levels are observed primarily in diseases in which monocytes or macrophages have been activated (Fuchs et al., 2009). The putative mechanisms by which neopterin contributes to the pathogenesis of heart failure is that of promoting oxidative stress, as reactive oxygen species and oxidative stress are known to depress myocardial contractility. More specifically, neopterin's interaction with the oxidant, peroxynitrite, may help to explain its role in the link between inflammation and heart failure (Trachtenberg & Hare, 2009). Neopterin measurements provide valuable information as an initial inflammatory marker and as a predictor for the progression of renal disease. In recent studies from our group, showed that neopterin is a marker of risk for the development of HF in patients with acute myocardial infarction and chronic stable angina (Dominguez-Rodriguez et al., 2006; Estevez-Loureiro, 2009; Dominguez-Rodriguez et al., 2010). Moreover, Nazer et al. in a large cohort showed that high neopterin levels were associated with increased risk of heart failure hospitalization over the next 2 years (Nazer et al., 2011). Along these lines, increased serum and urinary neopterin levels were found in patients with renal disease to correlate with serum creatinine levels (Lhee et al., 2006). In the present study, neopterin showed a negative correlation with GFR, a finding consistent with the report of Pecoits-Filho et al. (Pecoits-Filho et al., 2003) that neopterin levels were significantly higher in patients with a low GFR. Taken together, these observations suggest that high neopterin concentrations are a marker of impaired renal elimination of the marker, increased generation of neopterin or an adverse effect of inflammation on renal function (Pecoits-Filho et al., 2003).

Our study has limitations that should be considered. We did not measure other established markers of kidney function like Cystatin C (Lassus et al., 2011; Urbschat et al., 2011). The sample size was relatively small but even with this number of patients and after adjusting by different confounders, we were able to show, for the first time, that neopterin levels are an independent predictor of WRF in patients with ADHF. These findings may have clinical importance and warrant confirmation in larger clinical trials.

Declaration of interest

The authors have no conflict of interests.

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