Elevated Serum Neopterin Predicts Future Cardiac Adverse Events in Patients with Angina Pectoris

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Introduction: Neopterin, a pteridine derivative secreted by activated macrophages, has been shown to be associated with vulnerable coronary stenoses in patients with unstable angina. Neopterin has also been associated with coronary artery disease progression.

Objective: We sought to assess the prognostic significance of serum neopterin concentrations in patients with angina pectoris.

Material and Methods: We carried out a 1-year follow up study in 384 consecutive patients with angina pectoris (297 stable and 87 unstable). The primary study end-point was the composite of nonfatal myocardial infarction, class IIIb unstable angina and cardiac death. Serum neopterin was measured using a commercially available immunoassay (ELISA Kit, IBL, Hamburg , Germany ). Angiographic extent and severity of coronary artery disease were assessed and scored according to a validated method.

Results: Seventy four patients (19%) developed at least one major adverse coronary event. Serum neopterin levels were higher in patients with events compared to those without events (6.9 [4.8 to 8.3] vs 5.7 [4.1 to 7.6]; P=0.02). Only neopterin (P= 0.015), number of diseased vessels with =50% reduction in lumen diameter (P=0.005) and a history of MI (P<0.0001) remained independent predictors of the combined end-point. There was a significant gradual increase in the number of adverse events during the one-year follow-up with increasing of neopterin tertiles (p<0.001). After adjustment using binary logistic regression, patients in the highest tertile of neopterin distribution (>7 nmol/L) had an almost 3-fold higher risk of adverse cardiovascular events (OR 2.9 [1.4 to 6.2] CI 95%; P=0.006) compared to those in the lowest tertile (<4.8 nmol/L).

Conclusions: Neopterin is an independent predictor of adverse cardiac events in patients with angina pectoris. Our results suggest that this marker of macrophage activation and atherosclerotic disease activity may be useful for risk stratification in patients with coronary artery disease.

INTRODUCTION

There is increasing evidence that inflammation plays an important role in atherogenesis and may determine plaque vulnerability [1]. Macrophages have been shown to play a role in the disruption of the fibrous cap of atherosclerotic plaques that leads to the development of acute coronary events. Plaque disruption generally occurs at sites where the fibrous cap is thinnest and most heavily infiltrated with macrophage-derived foam cells. Neopterin, a pteridine derivative and a byproduct of the guanosine triphosphate-biopterin pathway, is produced by activated macrophages and is thought to represent a marker of immune activation and macrophage activity [2]. Neopterin also enhances the inflammatory activity within vulnerable plaques and stimulates gene transcription for inducible nitric oxide (iNOS), which releases unstable cytotoxic NO free radical.

Previous studies from our group showed that serum neopterin levels are elevated in patients with ACS and associated with the presence of complex vulnerable coronary lesions in patients with unstable angina [3-6]. We have also shown that high serum neopterin levels predict rapid CAD progression [7] and acute coronary events in patients with chronic stable angina (CSA) [8]. Neopterin also predicted cardiovascular
risk in hypertensive patients without obstructive coronary artery disease [9].

**OBJECTIVE**
We sought to prospectively assess the prognostic role of serum neopterin concentrations in patients with angina pectoris.

**MATERIAL AND METHODS**

**Patient selection**
We studied 384 consecutive patients (mean age 63 ± 10 years, 240 (63%) men) admitted to our institution for the assessment of angina pectoris. Eighty seven (23%) patients had ACS without ST-segment elevation and 297 (77%) had CSA. The patients' clinical management and the decision to proceed to cardiac angiography was left to the discretion of the managing cardiologist who was unaware of results regarding inflammation markers. None of the patients included in the study had ongoing systemic or cardiac inflammatory processes. All patients gave written informed consent before study entry and the study was approved by the local research ethics committee.

**Clinical characterization, follow-up and study end-points**
After recruitment and baseline characterization all patients were followed up for one year. Major clinical events during follow up, considered to represent study end-points, were: non-fatal AMI (defined according to World Health Organisation criteria as raised cardiac enzymes, characteristic ECG changes and prolonged typical chest pain), hospital admission with Braunwald's class IIIb unstable angina requiring medical treatment and/or urgent revascularization and cardiac death.

**Biochemical measurements**
For biochemical measurements, venous blood was collected from CSA patients at the time of diagnostic coronary angiography. In ACS patients blood samples were drawn at admission to Coronary Care Unit.

**Angiographic analyses**
Coronary angiography was carried out according to the Judkins technique, and images of the coronary tree were obtained in routine, standardized projections with the digital Philips Integris 3000 system (Philips, Holland), using an automated quantitative coronary artery stenosis assessment programme in all patients. Two experienced cardiologists who had no knowledge of the patients' clinical characteristics and biochemical results reviewed all angiographic images.

Coronary angiograms were scored according to the system of Sullivan et al. as described in previous studies from our group [3,6,8].

**Statistical analysis**
Results for normally distributed continuous variables are expressed as the mean value ± standard deviation (SD), and continuous variables with non-normal distribution are presented as median values (interquartile intervals). Differences between groups were assessed by unpaired t test and the Mann-Whitney U test for continuous variables, as appropriate, and chi-square testing was used for discrete variables. We assessed independent predictors of end-point using a binary logistic regression analysis and classified patients into three groups according to the tertiles of neopterin values upon study entry. Differences were considered to be statistically significant if the null hypothesis could be rejected with >95% confidence. The SPSS 11.0 statistical software package (SPSS Inc. Chicago. Illinois ) was used for all calculations.

**RESULTS**
Seventy four patients (19%) suffered events during the one-year follow-up. Serum neopterin levels were higher in patients with events compared to those without events (6.9 [4.8 to 8.3] vs 5.7 [4.1 to 7.6]; P=0.02). Univariate analysis revealed that neopterin serum concentration (P=0.02), number of diseased vessels with ≥50% reduction in lumen diameter (P=0.001) and a history of previous MI (P=0.004) were
associated with the development of the combined end-point. We performed forward stepwise binary logistic regression analyses where we included these variables, age, gender and the variables shown to have a relationship (P<0.20) with adverse events in the univariate analysis. Only neopterin (P= 0.015), number of diseased vessels with =50% reduction in lumen diameter (P=0.005) and a history of MI (P<0.0001) remained independent predictors of the combined end-point. Moreover, there was a significant gradual increase in the number of adverse events during the one-year follow-up with increasing of neopterin tertiles (p=0.01). Patients in the highest tertile (>7 nmol/L) of neopterin distribution had an almost 3-fold higher risk of adverse cardiovascular events (OR 2.9 [1.4 - 6.2] CI 95%; P=0.006) compared to those in the lowest tertile (<4.8 nmol/L) after multivariate analysis (figure 1).

**DISCUSSION**

The results of our study show that neopterin, a marker of macrophage activation, predicts adverse cardiovascular events during follow-up in patients with CAD. This is independent of the severity of the underlying coronary atheromatous disease. Compared with patients without cardiovascular events at one-year follow-up, those who developed the combined end-point of cardiac death, class IIIb unstable angina and non-fatal myocardial infarction had significantly higher levels of serum neopterin. Thus, neopterin may be a useful marker of risk in patients with CAD.

Our results confirm and expand previous findings from our group [8,9] and others regarding the predictive

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**figure 1:** Percentage of patients with events at follow-up regarding neopterin concentration tertiles. There was a significant gradual increase in the number of adverse events during the one-year follow-up with increasing of neopterin tertiles (P=0.01). Patients in the highest tertile of neopterin distribution had an almost 3-fold higher risk of adverse cardiovascular events (OR 2.9 [1.4 - 6.2] CI 95%; P=0.006) compared to those in the lowest tertile (<4.8 nmol/L) after multivariate analysis.
role of neopterin in ischemic heart disease. Results in the present study also suggest the role of monocyte/macrophage activation in the pathogenesis of acute coronary events.

Neopterin, inflammation and immune system activation.
Neopterin has been suggested to be a marker of atheromatous plaque activity. The relationship between serum neopterin concentration and angiographically complex coronary artery stenosis in patients with unstable angina was previously assessed by our group. We reported a significant association between circulating neopterin levels and the number of angiographically complex stenoses in patients with ACS [3,6]. Complex stenoses are known to represent vulnerable or disrupted atheromatous plaques. Moreover, we found that serum neopterin levels were higher in patients with AMI as compared to both patients with chronic CAD and normal control subjects. Schumacher et al, also reported elevated serum neopterin levels in patients with AMI, compared with patients with CSA or healthy control subjects. Elevated serum levels of neopterin in patients with ACS were not found to correlate with markers of myocardial injury such as creatine kinase, CK-MB isoenzyme or troponin I. Therefore, rather than a marker of myocardial necrosis, neopterin levels are most probably the expression of immune activation and related inflammatory mechanisms that lead to acute coronary events.

As also suggested for CRP, it is likely that the predictive ability of neopterin observed in our study and others may also indicate that neopterin is not only a marker of CAD activity, but may also play a pathogenic role in CAD. Neopterin has been shown to be involved in the activation of both constitutive and inducible NO synthase. Therefore, neopterin stimulates nuclear factor-κB (NF-κB) translocation to the nucleus, promoting expression of pro-inflammatory genes, adhesion molecules, tissue factor and other substances implicated in the inflammatory activity within the arterial wall.

Neopterin and severity/extent of coronary artery disease: Although studies have reported an association between neopterin and extent of atherosclerosis, i.e. peripheral vascular occlusions and carotid atherosclerosis, serum neopterin levels in our study did not correlate with severity or extent of CAD. Our data suggest that neopterin may be a marker of inflammatory coronary disease activity rather than a measure of the anatomic extent of the coronary atheromatous process. This finding is also in agreement with Schumacher et al.´s observations that serum neopterin levels in patients with CSA did not correlate with the number of diseased coronary vessels.

Limitations of the study: The main limitation of this study is the relatively small size of the patient population investigated. The lack of statistical power due to the small sample size may explain why hs-CRP levels did not differ significantly between patients with events at follow-up compared to those without events.

CONCLUSIONS
Our study shows that serum neopterin concentrations are associated with the development of adverse cardiovascular events in patients with CAD. This association was independent of the severity of CAD. Neopterin may be a useful marker of risk of future coronary events in patients with stable CAD. Neopterin better than CRP in this study was associated with the development of adverse outcomes in patients with CAD. Reasons for differences are speculative and deserve testing in larger studies.

BIBLIOGRAPHY


Publication: October 2005

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