Original Paper

Does Neutrophil Gelatinase-Associated Lipocalin Have Prognostic Value in Patients with Stable Angina Undergoing Elective PCI? A 3-Year Follow-Up Study

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Key Words

Neutrophil gelatinase-associated lipocalin • Stable angina • Percutaneous coronary intervention • Mortality

Abstract

Background: Neutrophil gelatinase-associated lipocalin (NGAL), a widely accepted diagnostic marker of acute renal injury (AKI) may be involved in the development of atherosclerosis.

Purpose: To assess the prognostic significance of serum and urinary NGAL and serum cystatin C in patients with stable angina undergoing percutaneous coronary intervention (PCI) on a 3-year follow-up. **Methods:** We included patients with stable angina undergoing PCI. Serum NGAL and cystatin C were evaluated before and 4h, 8h after PCI. Urinary NGAL was evaluated before and 12h and 24h after the procedure. The primary end-point was all-cause mortality on a 3-year follow-up. **Results:** Among 132 patients there were 63% of males (mean age 64.5±9.8 years). Mean eGFR was 86.2±28.5 ml/min. During follow-up 8% of the patients died. All-cause mortality was significantly higher in patients with increased urinary NGAL concentration 12h after PCI (p=0.04). Urinary NGAL 12h after PCI correlated with eGFR (p<0.05), with serum NGAL evaluated before and 4h and 8h after PCI (p<0.05) and with increased serum cystatin C evaluated 4 hours after PCI (p<0.05). **Conclusions:** Increased urinary NGAL concentration is a strong predictor of mortality in patients with stable angina who undergo PCI and may be used for the risk stratification in this population.

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Introduction

Neutrophil gelatinase-associated lipocalin (NGAL) is a glycoprotein stored in granules of neutrophils and is released by renal tubular cells in response to inflammation [1]. It has been shown to be an early and specific indicator of acute kidney injury (AKI) [2, 3] and may be a useful predictor of progression of chronic kidney disease (CKD) [4].

Furthermore, NGAL is also expressed in endothelial cells and may be involved in the development of atherosclerosis [5]. It could be increased in the presence of coronary artery disease (CAD) and may be a useful prognostic marker in patients with ischemic heart disease (IHD).

The aim of the present study was to assess the prognostic value of plasma and urinary NGAL in patients with stable angina who underwent elective percutaneous coronary intervention (PCI) on a 3-year follow-up.

Materials and Methods

Study population

We included in the study 132 consecutive patients with stable angina undergoing elective PCI admitted to the Invasive Cardiology Department. All the patients were given intravenous (IV) infusions of either NaHCO₃ or 0.9% NaCl within 24 hours after the procedure. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, and was approved by the local ethics committee.

Laboratory methods

Serum and urinary NGAL and cystatin C were evaluated using commercially available research-based ELISA assay from ANTIBODYSHOP (Gentofte, Denmark) and Dade Behring (Marburg, Germany), respectively. Serum NGAL and cystatin C were evaluated before and 4h, 8h after PCI. Urinary NGAL was evaluated before and 12h and 24h after the procedure. Serum creatinine was assessed using standard laboratory methods before and 24h after PCI.

Echocardiographic analysis

Left ventricular ejection fraction (LVEF) was assessed by transthoracic echocardiography using the modified biplane Simpson's method (Philips Ultrasound System Sonos 5500 (MA, USA), equipped for harmonic imaging with a 3.6 MHz transducer) and was derived in accordance with the recommendations of the European Society of Echocardiography [6].

Follow-up

The primary end-point was all-cause mortality on a 3-year follow-up. All data were obtained from the Polish population registry in Bialystok (Podlasie Voivodship Office) or telephone contact with the patients.

Statistical analysis

Distribution of every variable was tested with Kolmogorow-Smirnov test. Afterward the Student's t test or the Mann-Whitney U test were used for statistical analysis where applicable. Additional analysis of correlations between non-categorical variables was performed using Pearson or Spearman tests, where applicable. Data are expressed as means and standard deviations (SD). A p value of less than 0.05 was considered as statistically significant. The statistic software StatSoft, STATISTICA (data analysis software system) version 10, was used.

Results

The baseline characteristics of the study population is presented in Table 1. Total mortality was evaluated during 1054 ± 159 days of follow-up. The elective PCI was successful in 97%. Mean contrast volume used during coronary angiography was 154.2 ± 84.2 ml.

Table 1. Clinical and laboratory characteristics of the population

	n=132	±SD
Male	63 %	
Age (years)	64,48	9,76
Body Mass Index (kg/m ²)	28,98	4,48
Hypertension	89 %	
Diabetes mellitus	25 %	
Hypercholesterolemia	32 %	
Hypertriglyceridemia	35 %	
Smoker	41%	
Prior myocardial infarction	36 %	
Prior stroke	8 %	
Prior PCI	58 %	
Prior CABG	36 %	
Heart rate (beats /min)	66	11
Blood pressure systolic (mmHg)	128	18
Blood pressure diastolic (mmHg)	74	12
Ejection fraction (%)	49	12
Serum creatinine 0h (mg/dl)	1	0,21
Serum creatinine 24h (mg/dl)	0,98	0,23
eGFR by MDRD 0h (ml/min/1.73m ²)	75,78	16,83
eGFR by MDRD 24h (ml/min/1.73m ²)	78,25	20,18
eGFR by CG 0h (ml/min/1.73m ²)	86,17	28,54
eGFR by CG 24h (ml/min/1.73m ²)	86,6	27,3
Contrast volume (ml)	154	84
Serum NGAL 0h (ng/ml)	66,86	28,3
Serum NGAL 4h (ng/ml)	61,73	20,62
Serum NGAL 8h (ng/ml)	68,54	33,3
Increased serum NGAL	34%	
Urinary NGAL 0h (ng/ml)	14,21	13,06
Urinary NGAL 12h (ng/ml)	14,91	15,88
Urinary NGAL 24h (ng/ml)	17,22	15,59
Increased urinary NGAL	48%	
Serum cistatin C 0h (mg/dl)	1040,52	331,66
Serum cistatin C 4h (mg/dl)	993,46	326,68
Serum cistatin C 8h (mg/dl)	1063,26	361,98
Follow-up (days)	1054,81	159,14
Mortality	8 %	

PCI- elective percutaneous coronary intervention; CABG- Coronary Artery Bypass Graft; eGFR- and estimated glomerular filtration rate; MDRD- Modification of Diet in Renal Disease; CG- Cockcroft-Gault; NGAL- Neutrophil gelatinase-associated lipocalin.

Urinary NGAL 12h after PCI correlated with eGFR by MDRD formula and Cockcroft-Gault formula ($r = -0.25$, $r = -0.24$, $p < 0.05$, respectively), with serum NGAL evaluated before and 4h and 8h after PCI ($r = 0.33$, $r = 0.23$, $r = 0.19$, $p < 0.05$, respectively) and with increased serum cystatin C evaluated 4 hours after PCI ($r = -0.32$, $p < 0.05$).

Serum NGAL 4h after PCI correlated with age ($r = -0.26$, $p < 0.05$), hemoglobin level ($r = -0.23$, $p < 0.05$), serum creatinine ($r = -0.24$, $p < 0.05$), eGFR by Cockcroft-Gault formula ($r = 0.25$, $p < 0.05$).

Cystatin C concentration 4h after PCI correlated with age ($r = 0.23$, $p < 0.05$), ejection fraction ($r = -0.29$, $p < 0.05$), hemoglobin level ($r = -0.26$, $p < 0.05$), serum NGAL 4 hours after PCI ($r = -0.26$, $p < 0.05$), serum creatinine ($r = 0.39$, $p < 0.05$), eGFR by MDRD formula and Cockcroft-Gault formula ($r = -0.46$, $r = -0.24$, $p < 0.05$, respectively), mean contrast volume ($r = 0.18$, $p < 0.05$) and serum NGAL 4h after PCI ($r = 0.34$, $p < 0.05$).

During follow-up 8% (n=10) of the patients died. All-cause mortality was significantly higher in patients with increased urinary NGAL concentration 12h after PCI (12 % vs 2%,

Fig. 1. Kaplan-Meier survival curve according to increased urinary NGAL level.

$p=0.04$) compared to those without increased concentration which is displayed on Kaplan-Meier curve (Fig. 1). Both groups did not differ significantly in clinical characteristics. The increased mortality was also observed in patients with increased serum NGAL concentration 4h after PCI in relation to no increased serum NGAL (9% vs 2%), but that difference was not statistically significant ($p=0.13$). There was also no significant increase in mortality in patients with rise in serum NGAL concentration 8h ($p=1.0$) after PCI or in urinary NGAL concentration 24h after procedure ($p=0.85$).

Cystatin C concentration 4h ($p=0.27$) and 8h ($p=0.84$) after PCI did not correlate with mortality.

Discussion

In this study we found that increased urinary NGAL concentration 12 hours after PCI predicts all-cause mortality in patients with stable angina on a 3-year follow-up. To our knowledge the present study demonstrates for the first time the use of NGAL in estimating the long-term mortality in this population.

NGAL, a widely accepted renal marker, is expressed in endothelial cells and may be involved in the development of atherosclerosis. There are several studies which show that serum NGAL concentration is significantly elevated in patients with angiographically-confirmed coronary artery disease compared to those with normal arteries [7, 8]. Furthermore, Zografos et al. observed statistically significant correlations between NGAL concentration and the number of diseased vessels and the severity of CAD defined by modified Gensini index [8].

The important aspect of NGAL is its prognostic value in ischemic heart disease. There are several studies which use NGAL for risk stratification in patients with unstable angina (UA) [9] and acute myocardial infarction (AMI) [10, 11], but its role in patients with stable angina was not established. Furthermore, most of the studies concentrate on short-term outcomes. Lindberg et al. [10] prospectively enrolled 584 patients admitted due to a ST-segment elevation myocardial infarction (STEMI). They found that high plasma NGAL concentration measured 30 minutes before PCI independently predicts all-cause mortality and major adverse cardiovascular events (MACE) after STEMI on a 2-year follow-up. In another recent

study investigators demonstrated that high NGAL concentration is a predictor of in-hospital and 1-year mortality and MACE in patients with STEMI [11].

The prognostic value of NGAL was also defined in patients with chronic heart failure (CHF). Bolignano et al. [12] observed that serum NGAL >783ng/ml was associated with significantly higher 2-year mortality. Another study showed that high plasma NGAL is a predictor of a cardiac death or transplantation in CHF patients in a 3-year follow-up [13].

Similarly, NGAL could be used as a prognostic marker in patients presenting with acutely decompensated heart failure (HF). In the GALANT multicentre prospective trial discharge plasma NGAL was a strong predictor of a 30-days outcome, such as death and hospital readmission [14]. In other study high serum NGAL concentration (>167.5 ng/mL) was associated with 2.7-fold increase in the risk of death and 2.9-fold increase in the risk of a combined end-point (death or hospital admission) on 3-month follow-up in acute heart failure (AHF) patients [15].

In patients with chronic kidney disease NGAL remains a strong predictor of worse prognosis. Recent prospective study of patients with stage 3 or 4 CKD showed that urinary NGAL-to-creatinine ratio is associated with the combined end-point (death or hospital admission) in a 3-month follow-up in acute heart failure or progression to end-stage renal disease (ESRD) in a 2-year follow-up [4].

Apart from NGAL cystatin C is a protein mainly used as a biomarker of kidney function or as a predictor of cardiovascular complications. There are several studies which demonstrated that cystatin C predicts all-cause mortality or cardiovascular events among patients with chronic heart disease [17-19]. However, in our group of patients we did not find any significant relationship between cystatin C concentration and long-term mortality.

Conclusion

Increased urinary NGAL concentration is a strong predictor of mortality in patients with stable angina who undergo PCI and may be used for the risk stratification in this population.

Conflict of Interest

The authors report no conflicts of interest.

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