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Urinary NGAL as Early Prediction Marker for Severe Coronary Artery Disease in St-Elevation Myocardial Infarction

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Abstract

Background: Neutrophil gelatinase associated lipocalin (NGAL), an acute phase protein expressed in endothelial cells and macrophages in atherosclerotic plaques, may be involved in development of atherosclerosis via endothelial dysfunction, inflammatory processes and matrix degradation leading to atherosclerotic plaque instability by modulating the activity of metalloproteinase 9. Our aim was to correlate urine NGAL with complexity and severity of angiographic lesions in patients of STEMI.

Methods and Materials: We prospectively included 50 STEMI patients who underwent primary angioplasty. Urine NGAL, other inflammatory markers and biochemical parameters were measured on admission. According to SYNTAX score the STEMI patients were divided into two groups: Low SYNTAX score (≤ 22), intermediate- high SYNTAX score (>22).

Results: In our study, majority of STEMI patients (76%) had lower NGAL level (<50 ng/ml). Urine NGAL level showed significant increased trend as duration of angina increases (p=0.011). NGAL was significantly reversely correlated with LVEF (p= 0.04). Patients with deranged renal function (creatinine ≥ 1.5 mg/dl) had significantly higher NGAL values (≥50 ng/ml p=0.011). Although in STEMI, NGAL was not significantly correlated with number of vessels involved, but patients with high SYNTAX score (>22) had significant higher NGAL values (≥50 ng/ml p=0.012).

Conclusion: NGAL is a novel biomarker which predicts severity and complexity of angiographic lesions in patients of STEMI.

Key words: Atherosclerosis; biomarker; coronary artery disease; Neutrophil gelatinase associated lipocalin.

Introduction

Acute coronary syndromes (ACS) represent one of the most significant clinical endpoints of coronary atherosclerosis. Cardiac injury induced by the acutely impaired coronary flow threatens both the patient 's quality of life and the life span.Due to the strong correlation between atherosclerosis and inflammation, the investigators believe that the inflammatory markers could be predictor for atherosclerosis. In fact, C-reactive protein (CRP), cytokines, interleukins, the leukocyte count and many other inflammatory markers have been demonstrated to be predictors of atherosclerosis.[1]

Neutrophil gelatinase-associated lipocalin (NGAL) is a glycoprotein of 25kDa molecular weight that is initially isolated from the neutrophils and covalently bound to matrix metalloproteinase-9a (MMP-9).[2] In recent years, NGAL has been considered mainly a predictor of acute kidney injury (AKI). In addition, NGAL has been associated with cell death, inflammation and matrix degradation

and there is increasing evidence forenhanced systemic and myocardial expression of NGAL after acute MI, supporting the role of inflammation in this entity.[3]

It was demonstrated that high NGAL levels were associated with increased mortality in patients with STEMI.[4] On the other hand, the association between the increased NGAL level in ACS patients and the severity, complexity and the clinical risk scores in coronary disease is not clear yet.This prospective observational study was carried out with the aim of finding out the role of urinary Neutrophil Gelatinase-Associated Lipocalin (NGAL) as marker and correlation of NGAL level with complexity and severity of angiographic lesions in patient of ST Elevation MI.

Materials and Methods

This study was a prospective single centre open label study carried out in the department of cardiology. 50 Patients admitted with ST elevation myocardial infarction who underwent primary angioplasty for STEMI within 24 hours from the onset of symptoms were primarily enrolled during April 2015 to February 2017 in the study. The study conforms to ethical principles guiding human research (such as the Declaration of Helsinki) and study has been approved by a local ethics committee.Written informed consent was taken prior to the procedure.

Laboratory Measurements

Venous blood samples were obtained on admission in the coronary care unit or in the emergency department before PCI. High-sensitivity C-reactive protein (Hs-CRP) levels were measured by the immune-nephelometric method. Other biochemical parameters including the lipid profile, serum creatinine, troponin, CPK-MB levels were measured using commercially available methods and kits.

Urine NGAL (neutrophil gelatinase-associated lipocalin) was measured by using the ARCHITECT urine assay following manufactures protocol. The normal reference range for urine NGAL is ≤65.0 ng/mL in females and ≤23.4 ng/mL in males (95% reference value).The cut-off of urine NGAL of 50 ng/ml was taken which was based on previous studies[3] which showed the significance of urine NGAL in predicting adverse outcomes in STEMI patients.

Coronary Angiography

Coronary angiography was done according to standard techniques through femoral or radial approach. Patients were divided in two groups based on type of CAD as SVD (single vessel disease) and multi-vessel CAD (involvement of at least two or three of the epicardial coronary arteries) & SYNTAX score method was used to evaluate the severity and the lesion complexity of coronary artery disease.

Statistical Analysis

All statistical analysis was performed in IBM SPSS version 20. Quantitative variables were expressed as the mean ± standard deviation and qualitative variables were expressed as percentage (%). A comparison of parametric values between two groups was performed using the independent sample t test. Categorical variables were compared using the chi-square test. A nominal significance was taken as a two tailed p value <0.05.

Results

Baseline characteristics of study population shows in Table: 1. Hypertension, diabetes mellitus (DM), smoking and dyslipidemia were prevalent in both high and low NGAL groups. However, the difference between the two groups was not statistically significant (p>0.05). Also no statistically significant difference between two groups regarding age was noted (p>0.05) shows in table 2.

Table 1: Baseline Characteristics of Study Population.

Variables	Groups	Number	%	NGAL mean ± SD
Age Group	31-40	7	14	39.27 ± 34.60
	41-50	11	22	18.88 ± 18.48
	51-60	17	34	42.66 ± 71.59
	61-70	13	26	47.02 ± 61.89
	71-80	2	4	47.70 ± 33.37
Male		39	78	40.21 ± 58.07
Female		11	22	31.49 ± 40.48
Hypertension		35	70	31.77 ± 42.56
Diabetes Mellitus-Ii		7	14	39.44 ± 69.41
Smokers		25	50	25.38 ± 28.46

In our study, we found no statistically significant difference between high and low NGAL groups regarding troponin, hs-CRP and total leukocyte count (p>0.05).But, we did find the significant difference between raised creatinine (>1.5mg/dl) and NGAL level (p<0.05) shows in table 3.

Table 2: Correlation of risk factors with urine NGAL level.

Variables	Low NGAL(n=38) <50 ng/ml (mean ± SD)	High NGAL(n=12) ≥50 ng/ml (mean ± SD)	p value
Age	53.71 ± 11.47	56.75 ± 12.77	0.44
DM n (%)	6 (16%)	1(8%)	0.86
Hypertension n (%)	28 (74%)	7 (58%)	0.52
Smoker n (%)	20 (53%)	5 (42%)	0.74
HDL	33.94 ± 8.54	33.83 ± 14.88	0.97
LDL	104.9 ± 47.23	84.3 ± 43.02	0.19
VLDL	24.98 ± 13.55	35.38 ± 31.71	0.29
Total Lipids	625.84 ± 90.96	664.0 ± 191.01	0.52
Triglycerides	123.21 ± 68.95	176.25 ± 159.00	0.29
Total cholesterol	155.38 ± 55.6	153.83 ± 56.98	0.93

*HDL-High density lipoprotein, †LDL- Low density lipoprotein, ‡VLDL Very low density lipoprotein.

Table 3: Correlation between NGAL level with troponin, inflammatory markers and S.creatinine levels.

Variables	Low NGAL (n=38) <50 ng/ml (mean ± SD)	High NGAL(n=12) ≥50 ng/ml (mean ± SD)	p value
Peak Troponin	12.725±18.475	9.738±14.595	0.612
hs-CRP	14.08±18.21	16.9±12.93	0.622
TLC	11280±3673	12197±2585	0.427
S.creatinine (>1.5mg/dl)	1 (3%)	4 (33%)	0.011

*NGAL-Neutrophilgelatinase-associated lipocalin, †Hs-CRP- high sensitivity C-reactive protein, ‡TLC-Total leukocyte count.

Table 4: Correlation between NGAL and Clinical profile of ST elevation MI.

Type of STEMI	Low NGAL(n=38) <50 ng/ml	High NGAL(n=12) ≥50 ng/ml	p value
AWMI	19(50%)	4(33.33%)	0.498
IWMI	19(50%)	8(66.67%)	
Window period	**N (%)**	**NGALlevel (mean ±SD)**	
< 3 hours	26 (52%)	30.40±40.48	0.011*
3-12 hours	21 (42%)	35.38±48.34	
12-24 hours	6 (12%)	127.06±145.00	
LV Dysfunction	**N (%)**	**NGAL level (mean ± SD)**	
EF ≥45	15 (30%)	24.61. ±19.05	0.04*
EF <45	35 (70%)	42.99±32.04	

*P value <0.05 shows statistically significant, †NGAL- Neutrophilgelatinase-associated lipocalin, ‡AWMI-Anterior wall myocardial infarction, §IWMI- Inferior wall myocardial infarction, || LV-left ventricle, ¶EF-ejection fraction.

Table 5: Correlation between NGAL and type of coronary artery disease (CAD) and SYNTAX score.

Type of CAD	N (%)	NGAL (mean ± SD)	p value
SVD	25(50%)	24.2±27.54	0.066
Multi-vessel CAD	25(50%)	52.38±69.64	
SYNTAX score	**N (%)**	**NGAL (mean ± SD)**	
Low (<22)	41 (82%)	29.409±38.81	0.012*
Intermediate-high (≥22)	9 (18%)	78.75±91.51	

*P value <0.05 shows statistically significant, †NGAL-Neutrophil gelatinase-associated lipocalin, ‡SVD-single vessel disease.

In our study, we did not find significant correlation between NGAL level and type of ST elevation MI (p 0.498). The correlation between duration of symptoms and NGAL level was found to statistically significant (p 0.01). Higher values were observed in group of patients presenting with window period of 12-24 hours. In our study, there is statistically significant reverse correlation between NGAL and ejection fraction (p =0.04) shows in table 4.

There was no significant correlation between NGAL and type of coronary artery disease (p>0 .05). In our study, we found statistically significant difference between low and intermediate-high SYNTAX score regarding NGAL level (p<0.05) shows in table 5. Even we did not find statistically significant correlation between Hs –CRP values and SYNTAX score [mean SYNTAX score in normal Hs-CRP group 13.63±8.07 vsmean SYNTAX score in high Hs-CRP group 15.38±11.11;(p=0.52)].

Discussion

In our study, 50 patients presented with STEMI within window period of 24 hours and who underwent primary angioplasty were taken and analysed in terms of risk factors, electrocardiographic and echocardiographic evaluation, biochemical investigations and coronary evaluation.

In our study, the incidence of STEMI was most common in 50-60 age group (34%) which is similar to other studies by Lindsberg et al, Akcay et al who also observed majority of STEMI in age group of 50-60 years.[5,6]

In our study, commonest risk factors for STEMI observed were hypertension (70% patients), smoking (50%) and diabetes mellitus (DM) in 14% of patients. These findings are comparable to other studies byKirbis et al and Kafkas et al.[3] We didn't find significant difference between both groups of NGAL regarding above mentioned risk factors (p >0.05). Studies by Lindsberg et al, Akcay et al and AzzaA Al-afifydidn't find significant association between NGAL level and associated risk factors like hypertension, DM, smoking & dyslipidemia.[5-7]

Out of 50 patients of STEMI majority (54%) presented with IWMI and 46% presented with AWMI. This finding is in contraindication to previous studies like Akcay et al, BurakAyca et al which observed AWMI as the most common type of STEMI. [6,8] This difference could be due to small sample size and non-randomized selection of patients in our study. Out of 50 patients of STEMI, patients presenting with window period between 12-24 hours had showed higher NGAL values with significant correlation between urine NGAL levels and duration of symptoms (p value 0.011). AzzaAAl- afify found no significant association of NGAL levels with duration of symptoms (p=0.72).[7] This difference can be explained as in this study, estimation of NGAL was done in urine sample while in previous study serum NGAL was used and they included patients with duration of angina less than 12 hours. In our study there is statistically significant reverse correlation between NGAL and EF level (P=0.04). Similar results were noted in previous studies.[3,5,6]

Cardiac markers like troponin levels were elevated in both groups of NGAL and there was no significant difference between them (p value 0.0612). Similar association of troponin with NGAL level was demonstrated in earlier studies.[3,5,6] Inflammatory markers like hs-CRP, total leukocyte count (TLC) were not significantly correlated with NGAL level (p>0.05). Studies like Lindsberg et al & Akcay et al had demonstrated the association of serum NGAL with CRP, while Kirbis et al did not find correlation of urine NGAL with CRP level.[3,5,6] This difference could be due to difference between serum and urinary estimation of NGAL level. NGAL protein is a promising biomarker to detect acute kidney injury (AKI). In our study, there was no significant difference of serum creatinine level between low & high NGAL groups (p value 0.107), but higher values of serum creatinine (≥1.5mg/dl) were significantly present in patients with high NGAL group (p value 0.011). This finding matches with findings of previous studies of STEMI.[3,5-7] Thus in STEMI patients higher values of NGAL are useful in predicting renal dysfunction.

In our study, NGAL level didn't correlate with type of MI. Present study didn't show significant difference between single vessel and multivessel group (p=0.066), though higher values of NGAL were present inmultivessel CAD. In study of STEMI patients, Lindsberg et alshowed no significant difference between low & high NGAL group regarding multi-vessel CAD (p=0.33).[5] While some studies done in NSTE-ACShad demonstrated the role NGAL in predicting multi-vessel CAD.[4,9] This difference of NGAL in predicting multivessel CAD in NSTE-ACS and STEMI patients could be due to different pathophysiology and involvement of multiple vessels in NSTE-ACS.

Present study showed higher NGAL level in intermediate-high SYNTAX score (>22) with significant difference with low SYNTAX score group (p value 0.012). Studies by Soylu et al, Zografos et al and Chao li et al, showed that plasma NGAL levels were positively and significantly correlated with SYNTAX score.[4,9,10] SYNTAX scoring is a significant grading method in terms of determining complexity and severity of coronary artery disease. Higher SYNTAX score indicates a higher atherosclerotic plaque load and the fact that local inflammatory response in plaque site is higher in complex lesions as compared to simple lesions. Thus increased SYNTAX score observed in this study may be related to a higher inflammatory condition.

Conclusion

NGAL is a novel biomarker, easy and rapid to measure. Although majority of patients with STEMI showed lower NGAL level (<50 ng/ml), the increased NGAL level correlated with angiographic risk score. Therefore, NGAL level measured on admission to hospital could be beneficial in angiographic risk assessment of STEMI patients. The study finding showed a potential for an expanded study and several measures of NGAL levels needed to identify the proper timing of measuring NGAL in order to improve its prognostic value in estimating complexity and severity of angiographic lesions in patients with STEMI.

Limitations of the study

This is a single center, non- randomized and non-blinded study. Selection bias may not be excluded. The number of subjects was relatively small, so

a large scale multicenter prospective study is necessary to confirm the results of the study.

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