Original article

Microalbuminuria and C-reactive protein as a predictor of coronary artery disease in patients of acute chest pain

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ABSTRACT

Microalbuminuria is a risk factor for cardiovascular disease. It is gaining importance as a marker of atherogenic milieu and indicates the target organ damage and can be a valuable tool in screening and identification of patients with cardiovascular disease. Markers of inflammation, such as C-reactive protein (CRP), were found to be related to cardiovascular disease (CVD) events in patients with chest pain. In addition, recent studies have shown that, in the case of atherosclerosis, increased levels of CRP, reflects inflammatory condition of vessel wall. In the present study, CRP and microalbuminuria were estimated in patients of acute chest pain. The patients were divided into two study groups (gp-1 patients of chest pain with CVD and gp-2 patients of chest pain of causes other than CVD) along with one healthy control group. It was found that microalbuminuria was higher in CVD patients (RR = 6.250, 95% CI 2.346–16.45, $P < 0.05$) and also CRP was much higher in CVD patients (RR = 13.667, 95% CI 4.528–41.253, $P < 0.05$) as compared to other two groups. Sensitivity, specificity and positive predictive value of CRP and microalbuminuria were also higher in gp-1 (CVD) patients as compared to other two groups. Therefore, CRP and microalbuminuria can be used as important biomarkers in screening CVD.

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1. Introduction

Chest pain is one of the most common challenges for the clinicians in the emergency department. Prospective data demonstrates that elevated C-reactive protein (CRP) appears to predict the risk of cardiovascular events. CRP is produced by liver and increases whenever there is an activation of immune system. Immune system cells secrete inflammatory molecules and CRP is produced in response to elevation of these inflammatory molecules.

Microalbuminuria refers to urinary albumin excretion (UAE) (30–300 mg/24 h) that is not detectable by routine methods. Data from Losartan intervention for end point study indicates that the relationship between urinary albumin excretion and cardiovascular risk holds true well below the levels currently used to define microalbuminuria. Furthermore, there is evidence that regression of left ventricular hypertrophy parallels the reduction of albuminuria and is related to it to some degree, regardless of blood pressure changes.¹ It has been reported that markers of inflammation such as C-reactive protein, Interleukin-6 and Tumor necrosis factor- α ,

indicate that low grade inflammation is associated with the progression of microalbuminuria and with an increased risk of atherosclerotic disease.² CRP stimulates production of tissue factor by mononuclear cells, the main initiator of blood coagulation.³ In addition, it has been suggested that CRP together with phospholipase A₂ may cause complement activation and promote phagocytosis of damaged cells by activated neutrophils. Unstable atherosclerotic plaques have an increased number of macrophages that seem to be most abundant in the fibrous cap overlying the core of atheroma within the vessel wall. Therefore, an elevated CRP signifies ongoing activation of inflammation that characterizes unstable coronary artery disease and may be one of the causal factors of instability.⁴ Microalbuminuria even in healthy individuals is a risk factor for chest pain associated with cardiovascular events. The pathophysiologic mechanism underlying the association between albumin excretion and CVD is not fully understood. One hypothesis is that microalbuminuria may be marker of CVD risk because it reflects subclinical vascular damage in the kidneys and other vascular beds. It may also signify systemic endothelial dysfunction that predisposes to future cardiovascular events. Based on this theory, periodic screening for microalbuminuria could allow early identification of vascular disease and help to stratify overall cardiovascular risk.

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2. Materials and methods

The study group comprised of 50 patients of acute chest pain of cardiovascular disease (CVD) (Group-1), 50 patients of acute chest pain secondary to causes other than CVD (Group-2) admitted to emergency department and 50 age and sex matched healthy control (Group-3). Patients excluded from the study were of respiratory disease like pulmonary embolism, pulmonary tuberculosis, and pleurisy, gastro-esophageal disease like gall bladder disease, peptic ulcer and diabetes mellitus, hypertension etc. A diagnosis of cardiovascular disease was made from relevant positive history and corroborative laboratory evidence such as EKG, Cardiac Biomarkers such as Cardiac Troponin I and T (measured at presentation and repeated again at 12–24 h), Creatine Kinase-MB, C-reactive protein, two-dimensional echocardiography. Five milliliter of venous blood sample was collected and sample for CRP analyzed immediately after admission and 4–6 h thereafter. Early morning midstream urine sample was collected and was analyzed for micro-albuminuria. Informed consent was taken from all the subjects. CRP was measured by quantitative turbidimetric method and micro-albuminuria was estimated by nephelometry. The cholesterol and CK-MB (Creatine Kinase Muscle Fraction) levels were also measured in all cases. Continuous variables are presented as mean $\pm$ standard deviation and analyzed using ANOVA and Chi-square test with $P < 0.05$ as minimum level of significance. The usefulness of microalbuminuria and CRP was evaluated in terms of sensitivity, specificity, and positive predictive value.

3. Results

CK-MB in Group-1 was 190.16 U/L, Group-2 was 10.04 U/L and Group-3 was 10.93 U/L ($P < 0.05$). Total cholesterol in Group-1 patients was 204.22 mg%, Group-2 was 155.08 mg% and Group-3 was 156.08 mg% ($P < 0.05$) (see Table 1). C-reactive protein (CRP) in serum in Group-1 was 30.350 mg/L, Group-2 was 33.678 mg/L and Group-3 was 3.444 mg/L ($P < 0.05$). Microalbuminuria in Group-1 was 35.795 mg/L, Group-2 was 17.340 mg/L and in Group-3 was 12.661 mg/L ($P < 0.05$) (Table 2).

The relative risk for positive outcome (CRP > 10 mg/L) in Group-1 was 13.667 with 95% confidence interval ranging from 4.528 to 41.253, with the associated $P < 0.05$. The relative risk of increased CRP in Group-2 (non-coronary) patients was 0.250 with confidence interval ranging from 0.135 to 0.463, with associated $P < 0.05$. Taking cut off value of CRP 10 mg/L, the sensitivity in Group-1 was 93%, specificity 83% and positive predictive value 93%. Sensitivity in Group-2 was 80%, specificity was 74% and positive predictive value was 80%.

The relative risk of positive outcome of microalbuminuria (> 30 mg/L) was 6.250 with 95% confidence interval ranging from 2.346 to 16.653 with associated $P < 0.05$. Taking cut off value of microalbuminuria 30 mg/L, the sensitivity in Group-1 was 86%, specificity 64% and positive predictive value 86% (see Table 2). The relative risk in Group-2 could not be calculated, as all the patients in this group were having normoalbuminuria.

Table 1
Laboratory profile of biochemical investigations.

Laboratory tests	Group-1 Mean $\pm$ SD	Group-2 Mean $\pm$ SD	Group-3 Mean $\pm$ SD	P-value
Cholesterol	204.22 $\pm$ 45.48 (117–287)	155.08 $\pm$ 17.98 (124–189)	156.80 $\pm$ 21.21 ^{a,b} (124–235)	<0.05
CK-MB	190.16 $\pm$ 92.62 (58–450)	10.04 $\pm$ 6.42 (0–24)	10.93 $\pm$ 5.64 ^{a,b} (0–20)	<0.05

The laboratory profiles of cholesterol and CK-MB among various groups.

^a Significance difference of gp-1 from gp-2 ($p < 0.05$).

^b Significance difference of gp-1 from gp-3 ($p < 0.05$).

Table 2
Laboratory profile of special investigations.

	Group-1 Mean $\pm$ S.D. (range)	Group-2 Mean $\pm$ S.D. (range)	Group-3 Mean $\pm$ S.D. (range)	P-value
CRP	30.350 $\pm$ 19.361 (4–80.9)	33.678 $\pm$ 27.073 (0.8–87.5)	3.449 $\pm$ 4.480 ^{b,c} (0.4–26)	<0.05
Microalbuminuria	35.795 $\pm$ 26.990	17.340 $\pm$ 14.889	12.661 $\pm$ 21.285 ^{a,b}	<0.05

*Significant at 5% level of significance ($P < 0.05$).

Statistically significant difference in mean CRP and microalbuminuria levels among various groups.

^a Significance difference of gp-1 from gp-2 ($P < 0.05$).

^b Significance difference of gp-1 from gp-3 ($P < 0.05$).

^c Significance difference of gp-2 from gp-3 ($P < 0.05$).

The relationship between C-reactive protein and urine for microalbumin was found to be equal to 0.314*which is significant at five percent level of significance. This correlation is found out by the method of Karl Pearson's coefficient method.

Mean value for urine for microalbumin in females is 35.8157 and P -value is 0.007. Mean value for urine for microalbumin in males is 36.0737 and P -value is 0.00. Since P -value is < 0.05 , it is statistically significant.

Mean value of C-reactive protein in females is 39.557 and P -value is 0.002. Mean value of CRP in males is 27.998 and P -value is 0.000. Since P -value is < 0.05 , it is statistically significant. P -value for microalbumin in urine and CRP in the age group 35–80 years is < 0.05 which is also statistically significant (Table 3).

4. Discussion

In the present study, we highlight the importance of future policies on screening for microalbuminuria and CRP for the management of chest pain as an independent risk factor for CVD. CRP is a marker of acute inflammation. In the present study, the relative risk for positive outcome (CRP > 10 mg/L) in Group-1 was 13.667 with 95% confidence interval ranging from 4.528 to 41.253, with the associated $P < 0.05$. There is 13-fold increase in CVD patients, and this is statistically significant. In the Cholesterol and Recurrent Events (CARE) trial, CRP was a predictor of recurrent coronary events in men and women who had already suffered a myocardial infarction. Those with CRP concentrations in the highest quintile had an 80% higher chance of developing another coronary event (RR = 1.77; 95% CI 1.1–2.9).⁵ For patients other than CVD (Group-2), there was 0.250-fold increased risk and that is statistically significant ($P < 0.05$). Researchers from British, Columbia, Canada showed

Table 3
Relation of urine for microalbumin and CRP with age.

Age		Mean	P-value
15–25	Microalbuminuria	39.2950	0.071
	CRP	50.300	0.151
25–35	Microalbuminuria	17.2767	0.342
	CRP	26.993	0.209
35–45	Microalbuminuria	28.0940	0.015*
	CRP	17.800	0.017*
45–55	Microalbuminuria	40.1250	0.00*
	CRP	37.914	0.00*
55–65	Microalbuminuria	36.8233	0.00*
	CRP	28.273	0.00*
65–80	Microalbuminuria	46.0700	0.007*
	CRP	27.750	0.006*

* P -value < 0.05 .

Comparing microalbuminuria and CRP adjusted to age and sex.

that patients who experienced progressive bronchial dysplasia had initial CRP levels that were 64% higher than those who did not experienced subsequent progression.⁶

In the present study, the relative risk of positive outcome of microalbuminuria (>30 mg/L) in Group-1 was 6.250 with 95% confidence interval ranging from 2.346 to 16.653 with associated $P < 0.05$. In Heart Outcomes Prevention (HOPE) trials, microalbuminuria was associated with an adjusted relative risk of 1.83 for major CV events, 2.09 for all-cause mortality and 3.23 for hospitalization for congestive heart failure, with a similar relative risk in subjects with or without diabetes.⁷ In our study, there was 6-fold increased risk of microalbuminuria in CVD patients, and this increase is statistically significant ($P < 0.05$). Damsgaard et al.⁸ reported a greater incidence of cardiovascular events in elderly nondiabetic individuals with increased urinary albumin excretion (UAE) than in those with normal UAE after a follow-up of 62–83 months.

Taking cut off value of microalbuminuria 30 mg/L, the sensitivity in Group-1 was 86%, specificity 64% and positive predictive value 86%. For CRP, the sensitivity in Group-1 was 93%, specificity 83% and positive predictive value 93%. Sensitivity in Group-2 was 80%, specificity was 74% and positive predictive value was 80%. As sensitivity, specificity and positive predictive value in non-coronary cases (Group-2) was less than coronary cases, CRP and microalbuminuria can be viewed as risk factors of CVD and have a predictive role.

Conflicts of Interest

All authors have none to declare.

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