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RESEARCH ARTICLE

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Enhanced serum levels of matrix Gla protein and bone morphogenetic protein in acute coronary syndrome patients

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Background: Vascular calcification has been found to be associated with increased risk of cardiovascular (CV) morbidity and mortality. Various bone-associated proteins have been suggested to be related with this process. In this study, we aimed to evaluate whether serum levels of bone morphogenic protein-4 (BMP-4) and matrix Gla protein (MGP) differed in patients who were found to have normal epicardial coronary arteries or a culprit lesion in the coronary angiography leading to acute coronary syndrome (ACS).

Methods: Patients admitted to emergency department with the diagnosis of ACS who underwent primary percutaneous coronary intervention (PCI) between October 2015 and April 2016 were consecutively recruited as the patient group. Age and gender-matched subjects who underwent coronary angiography following non-invasive ischemia assessment made the control group.

Results: A total of 90 subjects (63.00±14.02 years, 70% male) were included in this study. MGP (<0.001) and BMP-4 (<0.001) levels were significantly elevated when compared to subjects with normal coronary arteries. Fasting blood glucose (*P*=.024), HDL-cholesterol (*P*=.002), C-reactive protein (CRP) (*P*=.001) levels, and left ventricular ejection fraction (LVEF) (*P*=.021) were significantly correlated with serum MGP levels. HDL-cholesterol (*P*=.001) and CRP (*P*=.030) levels were also significantly correlated with serum BMP-4 levels. In the model including HDL-cholesterol, CRP, MGP, and BMP-4 levels, only MGP (odds ratio[OR]: 1.018, *P*=.019) and BMP-4 (OR: 1.313, *P*=.023) were found to be independently associated with ACS.

Conclusion: This study shows that serum BMP-4 and MGP are independently associated with ACS occurrence when adjusted for other CV risk factors. These biomarkers may have a diagnostic potential in ACS patients.

KEYWORDS

acute coronary syndrome, atherosclerosis, biomarker, bone morphogenetic protein, matrix Gla protein

1 | INTRODUCTION

Vascular calcification has been found to be associated with three- to fourfold increased risk of cardiovascular (CV) morbidity and mortality.[1] Calcium deposition in the coronary arteries, also referred to as coronary artery calcium (CAC), and its progression has been associated with future coronary heart disease (CHD) events, including myocardial infarction (MI).[2,3] Promotion of vascular calcification has been attributed to the de-differentiation of vascular smooth muscle cells (VSMCs) into osteoblast-like phenotype.[4] A number of studies have

demonstrated the presence of bone-associated proteins, such as osteopontin, osteocalcin, bone morphogenic protein (BMP)-2, osteonectin, and matrix Gla protein (MGP) in human calcified, atherosclerotic plaques.[5-9] In this study, we aimed to evaluate whether serum levels of BMP-4 and MGP differed in patients who were found to have normal epicardial coronary arteries or a culprit lesion in the coronary angiography leading to acute coronary syndrome (ACS).

2 | MATERIALS AND METHODS

2.1 | Study population

Patients admitted to emergency department with the diagnosis of ACS who underwent primary percutaneous coronary intervention (PCI) between October 2015 and April 2016 were consecutively recruited as the patient group. Age and gender-matched subjects who underwent coronary angiography following non-invasive ischemia assessment made the control group. Exclusion criteria were determined as a prior diagnosis of chronic kidney disease, disorders of calcium/phosphorus metabolism, chronic inflammatory disease (such as rheumatic, hematologic, or other autoimmune diseases), osteoporosis, infectious disease, and malignancies. Patient recruitment continued until there were 45 patients in each group. Sociodemographic characteristics, co-morbidities (such as hypertension, diabetes mellitus), and medications (such as beta-blockers, statins, angiotensin-converting enzyme inhibitors [ACEi]/angiotensin receptor blockers [ARBs]) were recorded in all patients. Laboratory examinations included complete blood count, renal function tests, lipid profile, and C-reactive protein (CRP) levels. Additionally, creatine kinase-myocardial band (CK-MB) and troponin-I (TrI) levels were checked in patients diagnosed with ACS. Transthoracic echocardiography was performed in all patients to record left ventricular end-diastolic diameter (LVEDD) and left ventricular ejection fraction (LVEF). The local ethics committee approved the study, and it conforms to Declaration of Helsinki. Written consent was obtained from all patients prior to involvement.

2.2 | Measurement of BMP-4 and MGP levels

Ten milliliters of peripheral venous blood samples were obtained from patients prior to coronary angiography and immediately centrifuged. Serum samples were immediately centrifuged and stored at −80°C until assayed. Prior to analysis, the frozen serum samples were rapidly thawed and brought to room temperature and assayed for BMP-4 and MGP using enzyme-linked immunosorbent assay (ELISA) kits [Human Bone morphogenetic protein 4 (BMP4) ELISA Kit, Shanghai Sunred Biological Technology Co., Shanghai, China and Human Matrix Gla Protein (MGP) ELISA Kit, Shanghai Sunred Biological Technology Co., Shanghai, China, respectively], according to the manufacturer's instructions.

2.3 | Statistical analysis

Normally distributed continuous parameters are presented as mean±standard deviation, and skewed continuous parameters are expressed as median (interquartile range defined as the difference between 25 and 75 percentiles). Categorical data are presented as frequencies and percentages, and compared with chi-square test. Comparison between two groups was made with the Student *t*-test and the Mann-Whitney *U* test for continuous parameters with and without normal distribution, respectively. Univariate and multivariate binomial logistic regression analysis was performed to determine whether serum BMP-4 and MGP levels were independently associated with ACS occurrence. Spearman correlation analysis was done to investigate the factors related with serum BMP-4 and MGP levels. Statistical analyses were performed using SPSS statistical software version 21.0 (SPSS Inc., Chicago, IL, USA). A 2-tailed $P<.05$ is considered statistically significant.

3 | RESULTS

A total of 90 subjects (63.00±14.02 years, 70% male) were included in this study. Of 45 subjects diagnosed with ACS, 15 (33.3%) had unstable angina, 14 (31.1%) had non-ST-segment elevation myocardial infarction (NSTEMI), and 16 (35.6) had ST-segment elevation myocardial infarction (STEMI). Baseline characteristics of the study population are shown in Table 1. Among baseline characteristics, co-morbidities or medications did not significantly differ between the age and gender-matched study (n=45) and control groups (n=45). Fasting blood glucose ($P=.026$) and CRP ($P<.001$) levels were significantly higher; HDL-cholesterol levels were significantly lower ($P<.001$) in the study group when compared to the controls. In the study group, MGP (<0.001) and BMP-4 (<0.001) levels were also significantly elevated when compared to subjects with normal coronary arteries. Comparison of serum MGP and BMP-4 levels regarding the presence of conventional cardiovascular risk factors and medications is given in Table 2. Serum MGP and BMP-4 levels did not significantly differ between patient groups when history of hypertension, diabetes mellitus, smoking, family history of coronary artery disease (CAD), or medication use (beta-blockers, statins, ACEi/ARBs) were taken into account ($P>.05$).

Correlation between baseline characteristics and serum MGP and BMP-4 levels are shown in Table 3. Fasting blood glucose ($r=.282$, $P=.024$*), HDL-cholesterol ($r=-.377$, $P=.002$), CRP ($r=.352$, $P=.001$) levels, and LVEF ($r=-.263$, $P=.021$) were significantly correlated with serum MGP levels. HDL-cholesterol ($r=-.398$, $P=.001$) and CRP ($r=.230$, $P=.030$) levels were also significantly correlated with serum BMP-4 levels.

Multivariate regression analysis for identifying associates of ACS is given in Table 4. In the model including HDL-cholesterol, CRP, MGP, and BMP-4, only MGP (odds ratio [OR]: 1.018, 95% confidence interval [CI]: 1.003-1.034, $P=.019$) and BMP-4 (OR: 1.313, 95% CI: 1.039-1.659, $P=.023$) were found to be independently associated with ACS.

4 | DISCUSSION

This is the first study in the literature evaluating serum BMP-4 and MGP levels in patients with ACS compared to patients with normal

TABLE 1 Baseline characteristics of the study population (n=90)

	Total population (n=90)	Normal coronary arteries (n=45)	Acute coronary syndrome (n=45)	*P* value
Age, years	63.00±14.02	66.13±10.71	64.73±13.28	.583
Gender: male n (%)	63 (70.0)	31 (68.9)	32 (71.1)	1.000
Hypertension n (%)	53 (58.9)	25 (55.6)	28 (62.2)	.669
Diabetes mellitus n (%)	40 (44.4)	15 (33.3)	25 (55.6)	.056
Smoking n (%)	11 (12.2)	2 (4.4)	9 (20.0)	.050
Family history of CAD n (%)	15 (16.7)	4 (8.9)	11 (24.4)	.087
Statin use n (%)	66 (77.3)	35 (77.8)	31 (68.9)	.475
Beta-blocker use n (%)	59 (65.6)	30 (66.7)	29 (64.4)	1.000
ACEi/ARB use n (%)	32 (38.9)	14 (31.1)	18 (40.0)	.509
Serum creatinine (mg/dL)	0.90 (0.76-1.07)	0.82 (0.76-1.00)	0.93 (0.79-1.10)	.227
Fasting blood glucose (mg/dL)	105.00 (89.50-125.25)	95.00 (85.00-114.00)	112.00 (100.50-140.50)	.026*
Total cholesterol (mg/dL)	190.50 (147.00-217.03)	199.00 (152.00-236.00)	174.00 (145.00-207.00)	.212
Triglyceride (mg/dL)	140.00 (110.00-188.50)	141.00 (110.00-200.50)	128.00 (112.00-174.00)	.729
LDL-cholesterol (mg/dL)	124.00 (100.50-148.00)	126.00 (101.00-145.50)	119.00 (100.00-154.00)	.806
HDL-cholesterol (mg/dL)	41.82 (34.16-52.00)	47.00 (39.00-57.75)	37.21 (29.11-41.00)	<.001*
Hemoglobin (g/dL)	13.85±1.36	13.65±0.99	14.06±1.66	.240
White blood cell count ($\times 10^3/\mu L$)	7.71 (6.10-11.08)	7.60 (6.10-11.30)	7.80 (6.60-10.10)	.874
Platelet count ($\times 10^3/\mu L$)	229.00 (193.00-289.00)	219.00 (188.50-290.00)	234.00 (204.25-281.25)	.705
CK-MB (ng/mL)				
Baseline	2.10 (1.61-3.92)	-	2.10 (1.61-3.92)	NA
Peak	2.80 (1.93-14.56)		2.80 (1.93-14.56)	
Troponin-T (ng/mL)				
Baseline	0.02 (0.01-0.07)	-	0.02 (.01-.07)	NA
Peak	0.03 (0.02-1.41)		0.03 (.02-1.41)	
C-reactive protein (mg/dL)	11.23 (4.71-19.88)	7.45 (2.55-13.94)	15.00 (8.57-33.57)	<.001*
Left ventricular end-diastolic diameter (cm)	5.01±.54	4.98±.60	5.03±.47	.644
LVEF, %	56.74±10.86	58.34±11.16	55.18±10.47	.203
MGP (mg/dL)	523.17 (314.42-801.08)	319.00 (242.34-430.67)	794.00 (554.84-1846.50)	<.001*
BMP-4 (mg/dL)	22.33 (14.91-36.78)	15.15 (9.85-19.59)	36.14 (27.69-78.92)	<.001*

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMP-4, bone morphogenic protein-4; CAD, coronary artery disease; CK-MB, creatine kinase-myocardial band; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; MGP, matrx Gla protein; NA, non-applicable.
*$P<.05$.

epicardial coronary arteries. Our study has demonstrated that levels of both BMP-4 and MGP were independently associated with ACS diagnosis and they were significantly correlated with several conventional CV risk factors.

The role of BMPs in vascular calcification and atherosclerosis has been investigated in previous studies. BMP-2 has been demonstrated to mediate human coronary artery smooth muscle cell (CASMC) calcification in a dose-dependent way, due to an increase in intracellular Ca^{2+} deposition.[10] Oscillatory shear stress, that occurs particularly in branching vessels, has been reported to induce BMP-4, which results in endothelial dysfunction and inflammation via nuclear factor-kB, nicotinamide adenine dinucleotide phosphate oxidase, and cyclooxygenase-2 upregulation,[11-13] which is shown to be restored by inhibition of BMP-4 in diabetic mice models.[14]

Both BMP-2 and BMP-4 expression have been shown to be increased in human atherosclerotic plaques and the overlying endothelium of early atherosclerotic lesions within the coronary artery.[12,15] Similarly, our study has demonstrated that serum BMP-4 levels were significantly elevated in patients with ACS and an independent association persisted when other CV risk factors were taken into account. BMP-4 levels also significantly correlated with another inflammatory marker, CRP.

However, controversial findings do also exist. For instance, in patients with type 2 diabetes, serum BMP-4 levels were found to be

TABLE 2 Comparison of serum MGP and BMP-4 levels regarding presence of conventional cardiovascular risk factors and medications

Variables		Serum MGP levels	*P* value	Serum BMP-4 levels	*P* value
Hypertension	−	522.33 (298.17-716.50)	.842	18.52 (13.78-32.29)	.579
	+	524.00 (329.00-847.33)		24.00 (15.59-39.80)	
Diabetes mellitus	−	445.67 (284.00-590.25)	.103	19.08 (14.44-32.25)	.109
	+	611.50 (381.92-954.42)		27.69 (16.64-59.63)	
Smoking	−	489.00 (300.67-790.67)	.533	21.78 (14.32-36.46)	.557
	+	605.67 (464.00-977.33)		32.17 (15.27-37.89)	
Family history of CAD	−	489.00 (300.67-784.00)	.459	21.78 (14.32-35.96)	.454
	+	604.00 (452.33-885.67)		26.70 (15.27-60.90)	
Beta-blockers	−	524.00 (347.33-847.33)	.488	22.57 (14.40-37.89)	.648
	+	522.33 (300.67-794.00)		21.78 (15.21-36.46)	
Statins	−	784.00 (423.17-1551.50)	.109	36.14 (19.83-82.45)	.058
	+	464.00 (300.67-626.50)		19.48 (14.50-32.45)	
ACEi/ARBs	−	492.34 (287.33-793.58)	.288	19.52 (14.32-34.54)	.166
	+	524.00 (379.42-834.00)		24.95 (15.51-47.73)	

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMP-4, bone morphogenic protein, CAD, coronary artery disease; MGP, matrix Gla protein.

TABLE 3 Correlation between baseline characteristics and serum MGP and BMP-4 levels

	MGP (mg/dL)		BMP-4 (mg/dL)	
Variables	*r*	*P*	*r*	*P*
Fasting blood glucose, mg/dL	.282	.024*	.191	.130
LDL-cholesterol, mg/dL	.052	.652	.017	.882
HDL-cholesterol, mg/dL	−.377	.002*	−.398	.001*
LVEF, %	−.263	.021*	−.071	.543
WBC count, x10^3/μL	.035	.748	−.027	.806
Platelet count, x10^3/μL	−.048	.656	−.043	.698
C-reactive protein (mg/dL)	.352	.001*	.230	.030*
Peak CK-MB (mg/dL)#	.047	.759	.112	.462
Peak troponin-T (mg/dL)#	.006	.968	.081	.596

r, Spearman's correlation coefficient; BMP-4, bone morphogenic protein-4; CK-MB, creatine kinase-myocardial band, HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; MGP, matrx Gla protein.

*$P<.05$.

#only in subjects with acute coronary syndrome.

inversely correlated with intima-media thickness and cardio-ankle vascular index, which are markers of subclinical atherosclerosis.[16] In a small study,[17] serum BMP-4 levels were increased in subjects with chronic kidney disease and CAD compared with those without CAD, but there was no difference among patients without chronic kidney disease. In a recent study, after adjustment for other CV risk factors, a high serum BMP-4 level was an independent predictor for a decreased risk of multivessel disease ($P=.01$) in 1.044 consecutive patients who underwent elective coronary angiography and PCI.[18] The available literature suggests that this condition may be attributed to BMP-4 deposition into the atherosclerotic vascular tissue.[12,15]

The matrix Gla protein, an inhibitor of vessel and cartilage calcification,[19,20] has also been shown to be strongly expressed in human calcified atherosclerotic plaques in previous studies. Due to its plaque calcification-modulating properties,[21] MGP gene expression has been suggested to be induced in response to atherosclerosis.[22]

A strong positive correlation between serum MGP concentrations and artery calcification has been reported in the rat, with threefold elevation in serum MGP in those with the greatest artery calcification,[23] and authors have suggested that this may be secondary to increased local synthesis of MGP for the purpose of slowing the progression of arterial calcification. Nevertheless, it has been observed that an increase in only serum levels of MGP, without a concomitant increase in its gene expression in the arterial walls, does not inhibit the ectopic mineralization observed in mice lacking MGP.[24] In accordance with some previous studies that showed elevated serum MGP levels in patients with severe atherosclerosis,[25,26] our study has demonstrated that serum MGP levels were significantly higher in patients with ACS. This may be due to the fact that plaque rupture and thrombosis are determined by the balance between plaque structural stress (PSS) and material strength, and degree of calcification of a plaque has a profound effect on PSS.[27] In addition, our study has shown that serum MGP levels were significantly correlated with several CV risk factors and were independently associated with ACS occurrence. This is similar to another study showing the association between MGP and individual CHD risk factors and the Framingham CHD risk score in men and women free of clinically apparent CHD.[28]

On the other hand, the available data from other studies in humans are conflicting. Decreased serum MGP levels have been found to be

TABLE 4 Multivariate regression analysis for identifying associates of ACS

	Univariate				Multivariate			
		95% CI				95%		
Variables	OR	Lower	Upper	*P* value	OR	Lower	Upper	*P*
Smoking	0.956	0.659	3.063	.210	-	-	-	-
Family history of CAD	3.316	0.850	11.361	.253	-	-	-	-
Fasting blood glucose	1.005	.993	1.016	.415	-	-	-	-
HDL-cholesterol	0.894	0.839	0.952	.001*	0.893	0.750	1.063	.203
C-reactive protein	1.076	1.031	1.123	.001*	1.062	0.966	1.168	.213
BMP-4 levels	1.316	1.161	1.491	<.001*	1.313	1.039	1.659	.023*
MGP levels	1.019	1.009	1.028	<.001*	1.018	1.003	1.034	.019*

ACS, acute coronary syndrome; BMP-4, bone morphogenic protein-4; CAD, coronary artery disease; CI, confidence interval; HDL, high-density lipoprotein; MGP, matrix Gla protein; OR, odds ratio.
*$P<.05$.

correlated with increased severity of CAC as assessed by computed tomography.[29]

4.1 | Study limitations

There are some limitations of this study. First, the lack of follow-up in the study population limits the complete assessment of the role of these biomarkers in the ACS process. Second, a larger study population would have increased the power of the study. Third, this study only reveals an association, not a causal relationship. Further prospective studies with larger population are necessary.

5 | CONCLUSION

This study shows that serum BMP-4 and MGP are independently associated with ACS occurrence when adjusted for other CV risk factors. These biomarkers may have a diagnostic potential in ACS patients.

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