



Predictive value of osteoprotegerin for detecting coronary artery calcification in symptomatic patients: correlation with extent of calcification detected by multidetector computed tomography

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Abstract

Introduction: Osteoprotegerin (OPG) could be a marker of vascular calcification extent. The purpose of this study was to evaluate relationships between OPG and coronary artery calcification (CAC) extent in an Iranian population.

Methods: A total of 151 patients with chest pain [107 males/44 females, mean age: 57.23 (30-85)] were enrolled, excluding patients with previously established coronary artery diseases. All underwent chest multidetector computed tomography (MDCT) for CAC scoring. Blood samples were collected for measurement of OPG. A potential relationship between CAC, OPG, age and number of involved coronary arteries was investigated, and a receiver-operating characteristic (ROC) curve was designed thereafter to identify a cut-off value of OPG that best predicted the presence of CAC.

Results: A total of 93 patients did not have CAC, who were younger than others. The mean age of patients with a different number of involved arteries was significantly different and is significantly correlated with a number of involved coronary arteries. The mean level of OPG differed by the number of calcified coronary arteries and is significantly correlated with the number of involved coronary arteries. The level of OPG had a weak but positive correlation with Ca score. ROC curve analysis showed that plasma OPG level had a fair prediction of CAC score, with an area under ROC curve of 0.62. The cut-off value best predicting CAC score was 59.1 pg/ml.

Conclusion: This study suggests that a serum level of OPG can fairly predict extent of coronary artery calcification in symptomatic population.

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Introduction

Cardiovascular diseases are among the leading causes of mortality and morbidity worldwide and circulatory system disease raise third

highest disability-adjusted life years among Iranians.¹ Researchers have been investigated specific risk factors, but the current factor assessment still does not provide a satisfactory

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screening tool. Despite the traditional risk factors, coronary artery calcium consistently do better, including models such as Framingham risk predicting future cardiovascular events.² Coronary artery calcium which represents calcified atherosclerosis in the coronary arteries has been shown to be the strongest predictor of future cardiovascular events particularly when considered together with traditional risk factors.² Investigations continue on this file especially for optimizing the value of identified factors and finding non-invasive and efficacious approaches for early detection.

Mechanisms underlying the lengthy process of vascular calcification and the acute course of plaque disruption are still unclear and so are the contributing factors and clinical consequences.³ However, new insights are emerging on a newly discovered group of bone-regulating molecules that belong to the tumor necrosis factor-related superfamily including osteoprotegerin (OPG).⁴ Several studies suggested that elevated serum levels of OPG were associated with the atherosclerotic vascular disease in men and women and in patients with different chronic diseases.⁵⁻⁸ On the basis of these experimental clinical data, OPG seems to be an important marker in the process of arterial diseases.

Non-invasive radiographic imaging techniques such as multidetector computed tomography (MDCT) make it possible to quantify the coronary artery calcium. Thus, give the opportunity to investigate the different aspects of the connection between risk markers and progression of coronary artery calcium. The aim of this study was to 1- investigate the relationship between serum level of OPG and the extent of CAC as the severity of calcification and number of coronary arteries involved and 2- estimate the appropriate cut-off value to predict the presence of coronary artery calcium in our population.

Methods

The patients were recruited from University Clinic of Tabriz University of Medical Sciences, Iran. The protocol was conducted according to the principles of the Declaration

of Helsinki and was approved by the Regional Ethical Committee.

Patients experiencing chest pain who were candidate for computed tomography angiography (CTA) by the attending cardiologist were enrolled in this study. A history of myocardial infarction, angioplasty or coronary bypass surgery and current unstable angina resulted in exclusion. Moreover, patients with established malignancy, serum creatinine more than 2 mg/dl, diabetes mellitus (DM), and current use of immunosuppressive agents or steroids were excluded because of the possible effect on serum level of OPG. According to the fact that there is a high prevalence of osteoporosis after menopause, and we could not evaluate them properly with bone densitometry, these patients were excluded as well.

According to results of a previous study reporting the mean values of OPG in patients with different levels of coronary artery involvement⁹ with a power of 80% and alpha of 0.05, the study sample was estimated to be 150 patients.

On the day of CTA after 12 hours fast, antecubital venous blood samples were drawn into vacuum tubes for assessment of OPG. OPG was determined by an enzyme-linked immunosorbent assay.

MDCT evaluations were performed by Siemens Somatom Sensation 64 (Siemens Healthcare, Malvern PA). Axial 0.6 mm images synchronized with patient electrocardiogram were acquired and reconstructed as sagittal and coronal images using maximum intensity projection and multiplanar reconstruction (MPR) techniques and curved MPR. Then, additional three-dimensional reconstructions were made using VRT, Inspace and vessel view (Syngo, Siemens' imaging software). These reconstructed images were reviewed for the presence of coronary artery calcification (CAC). Patients were divided into three groups based on the degree of occlusion: 1- No CAC, 2- < 60% narrowing in the artery as minor CAC and 3- > 60% narrowing in the artery as significant CAC including patients with one, two or three vessel involvement.

Calcium was quantified according to the Agatston method which is calculated in an area of at least 2 contiguous pixels with a CT density threshold of 130 Hounsfield units.¹⁰

Data are presented as prevalence, percentage and mean [standard deviation (SD)] were appropriate. After checking the normality of the distribution of the data with Kolmogorov-Smirnov test, data were analyzed by t-test and one-way ANOVA for quantitative data, or chi-square for qualitative data. A correlation between parameters was evaluated using Pearson’s r correlation. The receiver operating characteristic (ROC) curve was used to determine the cutting point for best specificity and sensitivity for serum level of OPG. A statistical analysis was done using SPSS software (version 16, SPSS Inc., Chicago, IL, USA). A P < 0.050 was considered to be significant.

Results

A total of 151 patients with chest pain were evaluated in this study aged between 30 and 85 years. These included 107 males with a mean age ± SD of 59.81 ± 13.37 and 44 females with a mean age ± SD of 50.97 ± 6.29. The mean age of males was significantly higher than females (P = 0.001).

A total of 93 patients did not have CAC, who were younger than others (P < 0.001). The mean age of patients with a different number of involved arteries was significantly different (P < 0.001) (Table 1). Patients with two CAC were older than patients with none or one CAC (P = 0.020, P < 0.001). Patients with three CAC were older than patients with no artery involvement as well (P < 0.001). A regression analysis showed that age of patients is significantly correlated with a number of involved coronary arteries (Table 1).

The mean value of serum OPG was 80.85 ± 13.87 pg/ml, ranging between 20 and 2000 pg/ml. The mean level of OPG differed by number of calcified coronary arteries (P = 0.017) (Table 1). The level of OPG in patients with no CAC was significantly different from that in patients with two (P = 0.040) and three CAC (P = 0.007). This value was different between patients with three CAC and one CAC as well (P = 0.006). A regression analysis showed that level of OPG is significantly correlated with number of involved coronary arteries (Table 1). A level of OPG had a weak but positive correlation with Ca score (rs = 0.2, P = 0.001).

ROC curve analysis (Figure 1) showed that plasma OPG level had a fair prediction of CAC score, with an area under ROC curve of 0.62. The cut-off value best predicting CAC score was 59.1 pg/ml (sensitivity = 60.3%; specificity = 59.1%). The diagnostic performance of OPG was further analyzed using other cut-off values (Table 2).

Discussion

OPG plays its major biological role by inhibition of the receptor activator of nuclear factor kappa B (RANK) stimulation of osteoclast differentiation and bone resorption¹¹ through binding to RANK ligand (RANKL) as a soluble decoy receptor.¹² From this combination, endothelial cells and vascular smooth muscle cells produce only OPG¹³ but both RANKL and RANK expression have been detected in atherosclerotic lesions.¹⁴ OPG probably blocks the interaction of RANK-RANKL and reduce arterial calcification.¹⁵ This seems to start early in the process of atherosclerosis and has given a valuable potential for OPG for clinical implications.

Table 1. Characteristics of patients according to the extent of coronary artery calcification (CAC)

Number of vessels involved	Number of patients	Age (year)		Level of OPG		Ca score	
		Mean ± SD	Significance	Mean ± SD	Significance	Mean ± SD	Significance
None	93	53.47 ± 11.28	rs = 0.425, P < 0.001	80.32 ± 21.22	rs = 0.48, P < 0.001	90.09 ± 2.67	rs = 0.73, P < 0.001
1	27	58.11 ± 11.29		55.52 ± 4.05		229.22 ± 3.78	
2	14	68.64 ± 8.71		114.48 ± 43.16			
3	17	67.05 ± 11.94		91.95 ± 20.95			

SD: Standard deviation; OPG: Osteoprotegerin

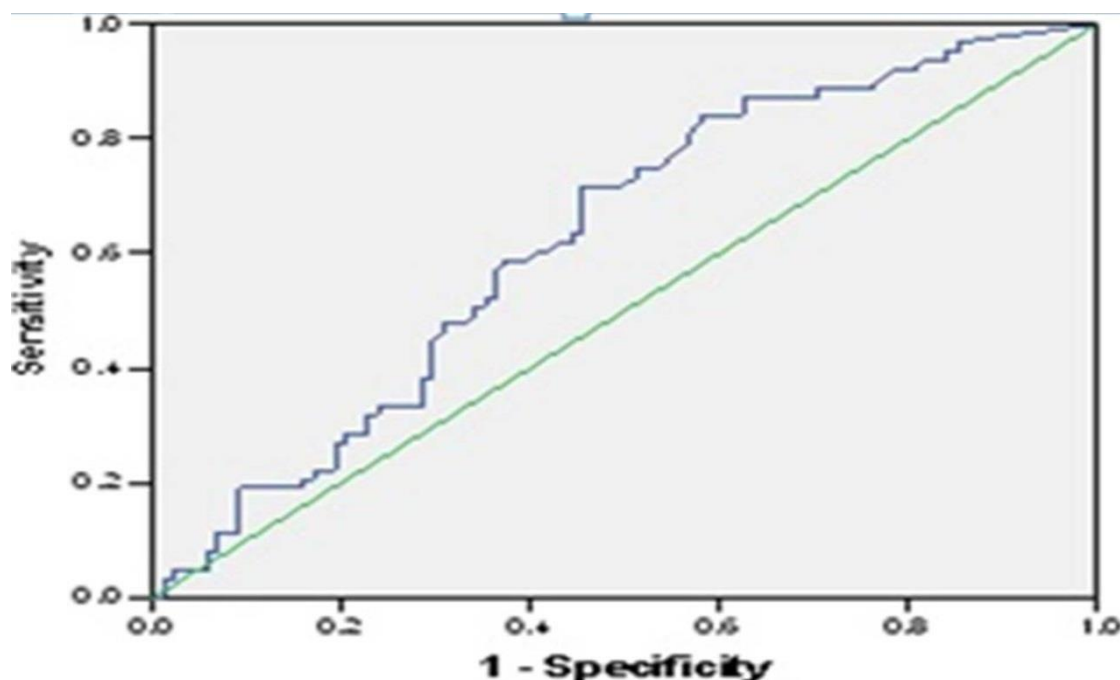


Figure 1. Receiver-operating characteristic curve of osteoprotegerin (OPG) plasma levels for the prediction of coronary artery calcifications (CAC) in 151 patients with stable chest pain

Table 2. Sensitivity and specificity of plasma osteoprotegerin to identify the presence of coronary artery calcification

OPG (pg/ml)	Sensitivity (%)	Specificity (%)
36.4	88	24
38.3	87	30
42.3	84	29
61.9	50	66
67.1	43	71

OPG: Osteoprotegerin

The current study suggested that the extent of CAC and number of involved arteries is related to age, serum level of OPG and Ca scoring in Iranian symptomatic patients with stable angina. We found that mean serum OPG levels increased significantly as the number of sclerotic coronary arteries increased. The distinctive point of our present study was that we performed a non-invasive method for detecting CAC. Results of this study are compatible with previous studies which detected CAC by coronary angiography,^{8,9} in terms, of the significant relation between level of OPG and extent of CAC.

Different study samples from all over the world could be of assistance final conclusion. There are a very few reports available from

Iranian population; however, the results are mostly compatible with different nations. The mean serum level of OPG is related to Korean people⁹ and Caucasian men.¹⁶ OPG also predicted both subclinical calcification and near-term cardiovascular events in uncomplicated patients with DM,¹⁷ silent myocardial ischemia in asymptomatic diabetic patients,¹⁸ chronic kidney disease⁷ and rheumatoid arthritis (RA)¹⁹ in western countries. All of these results indicate a helpful prognostic value for OPG despite ethnicity and clinical condition. Serum OPG seem to be clinically useful as a biochemical marker of vascular damage as well as burden of atherosclerotic disorders in general and studies also introduce serum OPG levels are an independent predictor of cardiovascular mortality in patients with stable coronary artery disease.²⁰

A recent study from our region investigated correlation of serum OPG with CAC detected by coronary angiography.²¹ A similar prediction value was reported for serum OPG when estimated by results of this invasive method; however a higher level of OPG is reported. It may be explained by

the fact that patients who were candidate for coronary angiography were probably in a poorer condition than our patients who were suggested an MDCT evaluation by the attending physician. These results also may indicate that the process of calcification begin even before OPG reaches these high levels, and OPG would still be helpful to detect the calcification.

This study had some limitations. It was not a population-based study and had a limited study sample; however, the sample is a very close to the daily practice, and the required number was calculated based on previous findings. We tried to overcome possible effect of osteoporosis by excluding elderly women. This could possible influence the difference between mean age of men and women in this study that was considered in

the analyses and should be considered in appraising the results.

Conclusion

Serum OPG is a valuable marker for coronary calcification in our population. Considering the cut-off value, this assessment should enable us to recognize patients at high-risk of vascular calcifications, and facilitate the decision for patients who should be managed aggressively.

Conflict of Interests

Authors have no conflict of interest.

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