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Could BMP-2 and BMP-7 be biomarkers of coronary artery disease? A pilot clinical study

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Abstract *Background:* Coronary artery calcification (CAC) is utilized as an important tool for the global risk assessment of cardiovascular events in individuals with intermediate risk. BMP-2 is a powerful inducer of bone formation and exposure to BMP-2 in the arteries leads to the loss of vascular smooth muscle cells (VSMC) markers and increase gene expression in favor of osteoblasts. BMP-7 is key factor in the bone and kidney and is suggested as inhibitor of vascular calcification. The main purpose of this clinical study was to find out the correlation between BMP-2 and BMP-7serum concentration and CAC in human for the first time.
Methods: In this study 84 patients with coronary artery disease who fulfilled inclusion and exclusion criteria, entered the study. For all patients a questionnaire consisting demographic data and traditional cardiovascular risk factors were completed. CT-Angiography was carried out to determine coronary artery calcium score and ELISA method was used for measuring BMP-2 and BMP-7serum concentrations.

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Results: There was a significant positive correlation between BMP-2 serum concentration and total CAC score and also CAC of right coronary artery (RCA), left anterior descending (LAD), circumflex (CX), left main coronary artery (LMCA) ($P < 0.05$). Similar result was found for BMP-7 serum concentration except in LMCA ($P > 0.05$).
Conclusion: Based on our results, we can suggest BMP-2 and BMP-7 serum concentration as a probable biomarker for coronary artery disease. However, more studies with higher sample size are necessary for its confirmation.

Introduction

Vascular calcification is a life threatening complication of cardiovascular disease and the statistics of patients with vascular calcification, especially in the elderly people and people with metabolic disorders, are on the rise. This process not only leads to increased mortality, but also leads to physical disabilities and a decrease in the quality of life.[1,2] It is an inevitable process particularly in the advanced stages of atherosclerosis which can create break in the vessels and cause the plaque rupture. Coronary artery calcification (CAC) is a surrogate marker for subclinical atherosclerosis and is known to reflect atherosclerotic burden. Increased coronary artery calcium score (CACS) correlates with the risk of cardiovascular disease.[3] CAC determined by electron beam-computed tomography (EBCT). EBCT was recently determined as strong predictor that comforts the prediction of future cardiovascular events particularly in intermediate risk subjects.[4]

Recent studies have provided impetus to shift from cellular interaction based calcification models to models emphasizing on the important role of extracellular matrix in calcification.

The bone mineralization controlling proteins are also involved in vascular calcification.[5] Bone morphogenic proteins (BMPs) are proteins associated with growth factors and subset of TGF-β superfamily. These proteins, along with the angiogenesis-inducing factors and through the paracrine-endothelial-mesenchymal pathway, maintain bone structure.[6] BMPs signaling path is so powerful in bone formation that its induction in the muscle tissue leads to the formation of false bone tissue in the place.[7] BMPs are expressed by endothelial cells, smooth muscle cells and foamy cells in atherosclerotic vascular areas.[8] Among the proteins in this family, BMP-2 and BMP4 And at a later stage BMP 5, 6, 7 have the highest association with vascular disease due to calcification.[8]

BMP-2 is a powerful inducer of bone formation and exposure to BMP-2 in the arteries leading to the loss of vascular smooth muscle cells (VSMC) markers and increase gene expression in favor of osteoblasts.[8]

Different molecular pathways have been reported for BMP-2 that SMAD pathway is the most important one. Actually, two SMAD dependent and non-SMAD dependent mechanism pathways are available that both of them trigger calcification process by induction of Osx, Runx2, and Dlx5 transcription.[9]

The second molecular pathway that is listed for BMP-2 stimulates Msx2 gene expression through induction of ALP and Runx2/Cbfa1 track progress to increases in favor of bone formation.[2,8,10]

BMP-7 is key factor in the bone and kidney, and genetically modified mice with a defect in BMP-7, have bone disorders and hypo-mineralization patterns, renal dysplasia and kidney growth inhibition, and visual defects.[8]

BMP-7 and its derivatives by stimulating phosphate storage by increasing smad6, smad7 and p_{21} Using the SMAD signaling pathway in the skeletal system lead to reduce plasma phosphate levels, which play a major role in vascular calcification and inhibits it and also induce the VSMC phenotype.[8,11]

According to this, we evaluated the BMP-2 and BMP-7 as diagnostic biomarkers in human to determine the extent of coronary artery calcification.

Methods

Patients

Eighty-three patients with diagnosis of coronary artery disease by angiography which was performed by the cardiologist, who aged higher than 40 years old, were enrolled in this study between November 2015 and March 2016. This test is the best way to detect CAD in the arteries, over 51% of which are blocked by atherosclerotic plaques and useful in detecting the vessels responsible for advanced CHD. However, it does not provide information about the artery wall and atherosclerosis may not be diagnosed that has not yet captured the duct. 12 patients with >50% coronary stenosis of at least one artery were considered as CAD+ and included in study. Patients with calcium and phosphor metabolic disorder or receiving medications which are effective on calcium and/or phosphate and immunosuppressant or antioxidant medications, intake of folic acid and methotrexate, malignancies, heart failure, hypo or hyper parathyroidisim, renal insufficiency, history of osteoarticular disorders and chronic inflammatory diseases, and acute infection during the study were excluded from the study. A questionnaire containing demographic data, laboratory data, drug and medical and familial history of cardiovascular risk factors was completed for all patients.

Patients were recruited from Cardiology ward of Razavi Hospital, Mashhad, Iran. This study was accepted by ethics