

Arginase as a new cardiac marker for diagnosis of coronary artery disease.

Abstract:

AIMS: The present study was undertaken to find the levels of AST, CK-MB and arginase in serum sample of patients under study and check effectiveness of arginase as a marker in acute coronary syndrome (ACS), and to find the correlation between AST and CK-MB with arginase in unstable angina (UA) and myocardial infarction (MI).

STUDY DESIGN: Case control study carried out at department of Biochemistry, B.J.Medical College Pune, Maharashtra, India, between Sept 2011-Dec 2013

METHODOLOGY: The study comprised of clinically diagnosed 60 patients: 30 of UA and 30 of MI. Age and sex matched 30 patients were studied as controls. Blood sample were collected from individual under study, serum was separated and used to estimate levels of CK-MB, AST and arginase.

RESULTS: The levels of AST, CK-MB and arginase were estimated and the results were compared with that of control. The levels of arginase were elevated significantly ($P < 0.001$) like AST and CK-MB in patients with MI as compared to UA. In the study there was no correlation observed between CK-MB and arginase in patients of UA or controls. The same was true with the levels of AST and arginase. On the other hand a strong positive correlation was found between CK-MB and AST with arginase in MI patients.

CONCLUSION: It can be concluded that like AST and CK-MB, arginase also increases with severity of the disease observed in ACS. Thus arginase can be used as sensitive marker to differentiate between UA and MI.

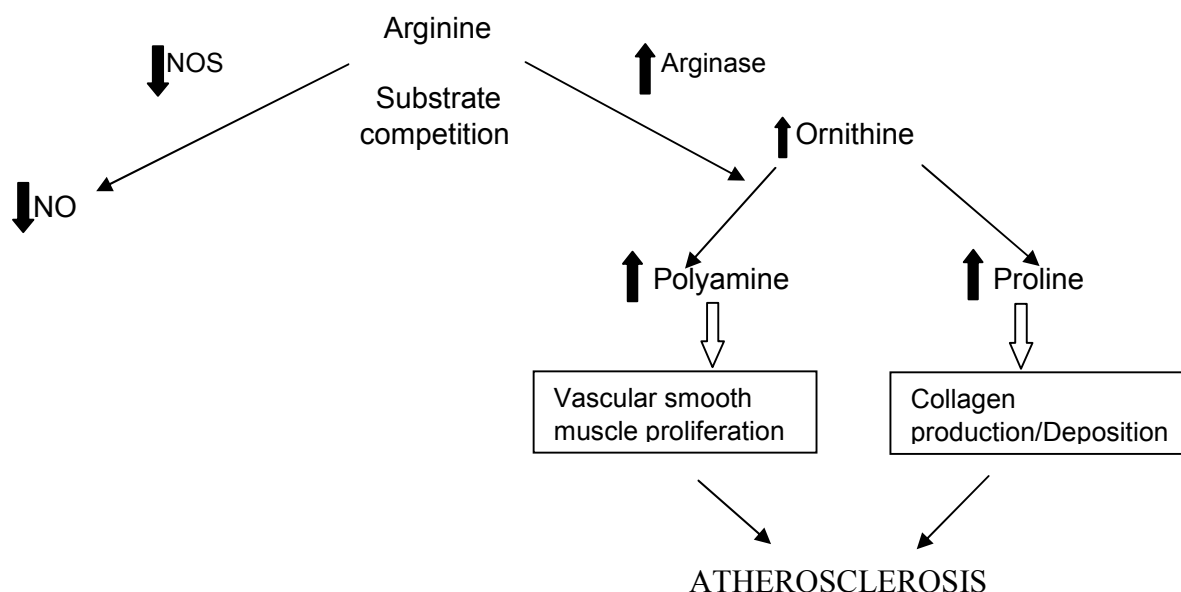
Keywords: Arginase, Coronary artery disease, Myocardial infarction

INTRODUCTION:

Coronary artery disease (CAD) is the leading cause of mortality and morbidity in the world and acute coronary syndrome (ACS) is the commonest amongst it. The prevalence of coronary artery disease (CAD) in India is 6.4% in urban and 2.5% in rural area. India has the highest burden of ACS. ACS is classified as non-ST elevation myocardial infarction (NSTEMI), ST elevation myocardial infarction (STEMI) and unstable angina (UA)¹. NSTEMI differs from UA in that ischemia is severe enough to produce myocardial necrosis. ACS is multifactorial disease and the predominant cause of ACS, in more than 90% of patients is atheromatous plaque rupture, fissuring, or erosion of an unstable atherosclerotic plaque. This exposes thrombogenic matrix proteins and promotes platelet accumulation and local fibrin generation. With repeated cycles of plaque injury and thrombus formation, progressive stenosis of vessel lumen occurs, leading to marked reduction in blood flow and transient tissue ischemia (UA) or total thrombotic occlusion of artery and tissue infarction (AMI)². Vascular homeostasis protects body from

these changes and is maintained by inhibiting vascular tone, platelet aggregation and inflammation. These functions are performed by synthesizing a molecule called Nitric oxide (NO) by vascular smooth muscle cells. Vasodilatory function of NO helps in maintaining vascular homeostasis. NO is synthesized from L- arginine by enzyme nitric oxide synthase (NOS). L- arginine is also a substrate for enzyme arginase. Thus these two enzymes compete with each other for the substrate. Increased arginase decreases NO production and diverts L-arginine to form ornithine. Ornithine forms polyamines and proline which promote aberrant vessel wall remodeling and neointima formation leading to atherosclerosis Fig1. Increased activity of arginase indicates low activity of NOS and thus less production of NO³.

Role of Arginine in atherosclerosis



Thus arginine is related to NO production and decreased NO production is directly related to vasodilatation. This relationship led us to think that arginase could be marker of ACS. In addition to this, there is no ideal biomarker currently available for diagnosing the condition. The diagnosis of ACS is based on clinical symptoms, electrocardiographic (ECG) changes and characteristic pattern of changes in some serum enzymes like aspartate transaminases (AST), creatine kinase (CK-MB), lactate dehydrogenase etc. Keeping these facts in mind it seems that arginase can be a good marker of ACS but there is paucity in the literature regarding relation between increased arginase activity and ACS. So, the present study was undertaken to determine the levels of arginase and its effectiveness over traditional enzymes like AST and CK-MB in ACS so as to use arginase enzyme as a marker.

MATERIAL AND METHODS:

The study was conducted after Institutional ethical approval and with prior consent of the patients. The study comprised of clinically diagnosed 60 patients: 30 of UA and 30 of MI. Age and sex matched 30 patients were studied as controls.

Inclusion criteria- Chest pain, Breathlessness, ECG changes s/o ASC, No renal, liver or infectious disease.

Exclusion Criteria: Valvular Heart disease, Pericarditis, chest pain due to respiratory or gastrointestinal cause, alcoholics, psoriasis, arthritis, sickle cell disease and cancer.

5 ml blood sample was collected from individual under study, serum was separated and used to estimate levels of CK-MB⁴, AST⁵ and arginase⁶.

RESULTS AND DISCUSSION:

India has the highest burden of ACS in the world. ACS results primarily from diminished myocardial blood flow secondary to an occlusive or partially occlusive coronary artery thrombus. Currently there is no marker available to meet all of the criteria of ideal cardiac marker. Hence present study was carried out to find effectiveness of arginase as a marker in ACS. The levels of arginase were compared with that of AST and CK-MB in UA and MI (Table 1).

Observation and Result:

Table1: Shows levels of AST, CK-MB and Arginase in control group and groups of UA and MI

Group	AST(IU/L)	CK-MB (IU/L)	Arginase(IU/L)
Controls	19.11±6.18	12.62±5.78	2.20±0.86
UA	20.89±5.11	14.35±3.43	2.38±0.35
MI	*77.29±14.44	*122.87±21.89	*9.48±1.11

*P<0.001- highly significant

It was observed that levels of AST, CK-MB and arginase were increased significantly (P < 0.001) in patients with MI⁷. However this increase was not significant in patients with UA (P > 0.05). Thus the results of arginase were comparable with that of conventional enzyme markers of ACS i.e. serum AST^{8,9} and CK-MB¹⁰⁻¹². In addition to this increased levels of arginase reflects the status of NO[•] as increased levels of arginase inhibits production of NO[•]^{13,14}. This is achieved via several potential mechanisms, including competition with NOS for L-Arginine, uncoupling of NOS resulting in generation of NO[•] scavengers, superoxide and peroxynitrite, repression of translation and stability of iNOS protein, inhibition of iNOS via generation of urea and by sensitization of NOS to its endogenous inhibitor asymmetric dimethyl L-arginine¹⁵.

In present study, there was no correlation observed between CK-MB and AST with arginase in patients of UA or controls whereas a strong positive correlation was found between CK-MB and AST with arginase in MI patients (P value < 0.001). This indicates that like AST and CK-MB, arginase also increases with severity of the disease ACS.

Now a days enzyme arginase is considered as drug targets in MI as arginase inhibitors inhibit arginase and reciprocally elevate NO[•]; a vasodilator. Thus it helps in restoring endothelial functions and reducing vascular plaque burden. Hence arginase could be an important target in atherosclerosis therapy¹⁶ and its inhibition provides protection against myocardial injury¹⁷. This also supports our findings that arginase could be used as a marker of severity.

CONCLUSION: Arginase levels increase with severity of the ACS. Hence it can be a good, sensitive marker, to differentiate between UA and MI.

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