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Editorial Commentary

Heart-type fatty acid-binding protein (H-FABP) and coronary heart disease

Development of a simple, yet dependable and robust diagnostic marker in the diagnosis of acute coronary syndromes, especially in an emergency setting, is not only important but is also essential. Availability of such a test will ease the burden on any emergency department to arrive at accurate diagnosis to minimize possible errors of judgment. It is important that such a test needs to be highly specific, sensitive, and easy to perform. Though traditionally cardiac troponin T (cTnT) is used as a biomarker to diagnose acute coronary syndromes, it may not rise till 6 h after the onset of symptoms and may have to be repeated within 8–12 h after the onset of pain in order to confirm or negate the diagnosis. Hence, more accurate and dependable diagnostic test(s) that can detect coronary disease earlier than 6 h after the onset of chest pain are needed. Plasma levels of heart-type fatty acid-binding protein (H-FABP) seem to fill up such a gap. In the previous issue, Vupputuri et al.[1] outlined their experience with H-FABP in 54 patients presenting with acute ischemic chest pain and concluded that it could be used as an early marker, while cTnT could serve as a late marker for diagnosis of AMI before ECG changes become apparent. In this context, it is prudent to review briefly the structure, function, and clinical significance of H-FABP.

1. H-FABP

H-FABP, also known as mammary-derived growth inhibitor, is a protein that in humans is encoded by the *FABP3* gene, which is located on chromosome 1, with its specific location being 1p33-p32. H-FABP is a 51.2 kDa cytoplasmic protein that is composed of 133 amino acids and is released from myocardial cells following an ischemic episode.[2] Like the nine other distinct FABPs that have been identified, H-FABP is involved in active fatty acid metabolism, where it transports fatty acids from the cell membrane to mitochondria for oxidation. These FABPs are believed to participate in the uptake, intracellular metabolism, and/or transport of long-chain polyunsaturated fatty acids (PUFAs). FABPs have modulatory influence on cell growth and proliferation, and arrest growth of mammary epithelial cells. Immunoreactivity of H-FABP was detected in both ventricles and atria, in many striated muscles, parietal cells of the stomach, renal epithelial cells, acinar and ductal cells of the breast, ductal cells of the salivary gland, corpus luteum, Leydig cells of the testis, adipocytes, vascular endothelial cells, and terminally differentiated epithelia of the respiratory, intestinal, and urogenital tracts.[3,4] H-FABP was not detected in old infarcts of the heart and necrotic cardiomyocytes. Even morphologically normal cardiomyocytes did not show H-FABP 1 h after acute ischemic lesions[3] suggesting that these cardiomyocytes that appear to be apparently normal are in fact non-viable cells. In this context, it is noteworthy that exposure of primary cultures of rat neonatal myocytes to saturated fatty acids (C16:0 and C18:0) but not monounsaturated (C16:1 or C18:1) and polyunsaturated (C18:2, C18:3 and C20:4) resulted in cell death.[5,6] Furthermore, PUFAs enhanced the expression of FABPs, and the detrimental effect of saturated fatty acids was nullified by unsaturated fatty acids[5] indicating that one of the functions of H-FABP could be to transport PUFAs to myocardial cells and thus preserve their integrity. This is supported by the observation that mice lacking H-FABP showed severe defect in utilization of PUFAs and heart failed to efficiently take up plasma PUFAs and use it as the main fuel. H-FABP deficiency also led to acute exercise intolerance and localized cardiac hypertrophy.[7] These data are in agreement with the fact that H-FABP is needed for cardiac intracellular lipid transport and fuel selection and thus, plays a major role in metabolic homeostasis.[6] Thus, it is likely that release of H-FABP due to ischemia may further aggravate cardiomyocyte function and survival due to reduced or absent H-FABP that leads to inefficient transport PUFAs for use as fuel. In addition, those who have consumed increased amounts of saturated fatty acids and trans-fatty acids are more likely to be at increased risk of further aggravation of myocardial damage since saturated fatty acids and trans-fatty acids are toxic to myocardial cells.[5] This may explain the benefit of consuming PUFAs since they have been shown to nullify the toxic actions of saturated fatty acids on myocardial cells.

2. Measurement of H-FABP in coronary heart disease

In view of the importance of H-FABP in myocardial function, it is quite but natural that its measurement in the plasma formed a reliable test for myocardial ischemia. A sandwich enzyme-linked immunosorbent assay (ELISA) developed back in 1995 for H-FABP showed that the assay range was 0–250 ng/ml, the minimum detection limit of the assay was 1.25 ng/ml, and the plasma and urine H-FABP values were 3.65 ± 1.81 ng/ml and 3.20 ± 2.70 ng/ml, respectively in normal healthy subjects.[8] This ELISA test[8] mentioned above is more sensitive than the one used by Vupputuri et al.[1] Several studies performed since have clearly established that H-FABP is a reliable and early cardiac marker for diagnosis of acute myocardial infarction (AMI) soon after the onset of symptoms.[9] As a result of this reliability, several types of test systems were also developed to measure both plasma and urine H-FABP. In fact, there is now an attempt to use H-FABP measurement as a biomarker to detect or exclude an early-stage acute myocardial infarction (AMI), and results showed that combining H-FABP and cardiac troponin T (cTnT) provides the best performance for early AMI diagnosis.[10] Hence, it is time that measurement of H-FABP is done in all patients with chest pain coming to the emergency to exclude or confirm the diagnosis of acute coronary syndromes. Perhaps, development of a simpler method of detecting and measuring H-FABP may encourage even smaller hospitals (especially in India, where ELISA or other tests systems may not be available in rural hospitals) to use this test for the benefit of the patient. It is possible to develop a simple strip test for H-FABP (similar to glucose testing) that will encourage almost all hospitals to use it in their emergency department. But the usefulness of H-FABP in patients suspected of acute coronary syndrome is not without controversy. Based on the results of a prospective monocentre diagnostic accuracy study of H-FABP bedside point of care (CardioDetect®) and ELISA tests in acute coronary syndrome suspected patients presenting within 24 h of symptom onset to the emergency department, it was concluded that H-FABP testing improves diagnostic accuracy in addition to clinical findings and electrocardiography, but it is of no additional diagnostic value when hs-cTnT measurements are also available.[11] These results imply that additional studies are needed to confirm the usefulness of H-FABP in the emergency department. Hence, it is recommended that a larger number of patients (perhaps in thousands) and under different settings such as urban and semi-urban hospitals (small to midsize to large corporate and teaching hospitals) need to be studied to assess the utility of H-FABP.

3. H-FABP in other conditions

In addition to its use in diagnosing acute coronary syndromes, it is being realized that H-FABP may be useful to detect myocardial functional status in other conditions including congestive cardiac failure, sepsis, pulmonary thromboembolism,[12–14] etc. It is noteworthy that serum H-FABP concentrations are increased in non-alcoholic fatty liver disease (NAFLD) and metabolic syndrome,[15,16] suggesting that it (H-FABP) may serve as a marker of insulin resistance that is present and the existence of subclinical myocardial damage in these patients. This association of H-FABP with inflammatory conditions such as heart failure, coronary heart disease, sepsis, metabolic syndrome, NAFLD, and insulin resistance[17] is in close proximity to the similar association seen between these conditions and A-FABP (adipose-FABP).[18] It is interesting that both H-FABP and A-FABP are expressed in subcutaneous and intramuscular adipocytes[19] and the transcript of H-FABP in brown adipose tissue (BAT) was increased about 100-fold by cold exposure, whereas that in white adipose tissue (WAT) was negligible, and on treatment with norepinephrine (NE), transcript level of H-FABP was elevated markedly but that of A-FABP was not changed in brown adipocytes.[20] These results emphasize the involvement of H-FABP in the regulatory role of autonomic nervous system on adipose and cardiac tissues. Since catecholamines are pro-inflammatory in nature,[21] whereas acetylcholine, the principal neurotransmitter of parasympathetic nervous system, is anti-inflammatory in nature,[22] it is obvious that there is a close positive and negative feed-back regulation among catecholamines, acetylcholine, FABPs, inflammation, and inflammatory conditions. These interactions indicate that in acute coronary syndromes, it may be worthwhile to assess the plasma levels of A-FABP (in addition to H-FABP), cytokines, catecholamines, and adipokines to obtain a comprehensive picture of the underlying molecular mechanisms of the disease and their relationship to its progress and prognosis. Clinicians are uniquely suited to adopt such an approach to decipher and integrate the clinical picture with the underlying pathophysiology. I trust that clinicians such as Vupputuri et al.[1] would take such a route in their future endeavors.

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