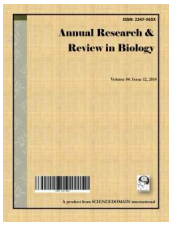

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Brief Review - Emerging Cardiac Biomarkers as Screening Tool for Atherosclerosis

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Authors' contributions

This work was carried out in collaboration between all authors. Author SA conceptualized and designed the study, wrote the first draft and reviewed the final version. Authors FSA and MA participated in analyzing it critically. Author NA managed the literature and references. All authors read and approved the final manuscript.

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ABSTRACT

Apart from the use of cardiac biomarker for diagnosing and monitoring Acute ischemic disease, an acute myocardial infarction (AMI) and Heart failure, the same biomarkers can also be used for predicting the chances of suffering from these diseases in future. In a way these can be used as screening biomarkers. Since the biomarkers, which are intracellular biomolecules, are released in to the peripheral circulation from necrosis of myocytes. Lipids and lipoproteins do have high value in assessing the risk of future cardiac disease, but are not produced by the heart and don't directly reflect the status of the heart, rather they simply provide a measurement of future risk of atherosclerosis. Cardiac biomarkers on the other hand can also provide or help in assesing the extent of damage that has been caused to the myocardium because of their specificity and rapid release or increase in the peripheral blood post injury to the myocardium, as well as their presence in plasma in low concentrations normally. Hence other than the classic cardiovascular risk markers like LDL-C, HDL-C, and triglycerides, presence in abnormal amounts of the emerging markers like

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apolipoprotein A1/apolipoprotein B100, Lp(a), oxidized LDL, LpPLA2, hsCRP, homocysteine, myeloperoxidase and as well as lipoprotein particle size and concentration can indicate, as well as predict myocardial stress more accurately. The probability of developing a cardiac disease is higher if a particular risk marker is in abnormal amounts. This, in no way means that the individual is certain to develop cardiac disease but is most likely to get the disease.

Keywords: High sensitivity C-reactive protein (hs-CRP); lipoprotein-associated phospholipase A2 - (LpPLA2); lipoprotein(a)- Lp[a],oxidized LDL.

1. INTRODUCTION

Atherosclerosis is one of the leading causes of heart disease and its presence is an important risk factor for events leading to acute myocardial infarction (AMI). In the past, atherosclerosis was described as a cholesterol and lipid storage phenomenon. Now, however, we know it is a more complicated inflammatory process of the arterial vessels; lipid particles and immune cells. Inflammatory cytokines, macrophages, lipids and lipoproteins instigate the creation of foam cells, which are deposited in the vessel wall and lead to narrowing of the artery. One of the major concerns of heart disease is that in 9 out of 10 individuals it is asymptomatic and when it does strike, leads to serious, often fatal, consequences. Use of radiography and echocardiography for predicting heart disease requires not only highly sophisticated equipment but also specialist interpretation; hence there is a need for noninvasive biochemical tests which can be easily interpreted to predict development of heart disease in future. Shortness of breath during active state, which is one of very initial clinical signs of cardiac problems is somewhat very similar to respiratory disease. Therefore, specific, sensitive, rapid and inexpensive blood tests for cardiac injury are desirable to differentiate a cardiac problem from respiratory problem. Apart from the conventional lipid profile, cardiac biomarkers can also provide information or help in assesing the extent of damage that has been caused to the myocardium. Cardiac biomarkers are specific, are produced in the heart and rapidly released or increase in the peripheral blood following injury to the myocardium. Previously, screening for cardiovascular disease (CVD) was based on risk factors like hyperlipidemia, obesity, and hypertension. However, approximately one half of AMIs occur in healthy men and women with normal or only slightly elevated plasma lipids. With new insights into cardiac disease emerging biomarkers like apolipoprotein A1/apolipoprotein B100, Lp(a), oxidized LDL, LpPLA2, hsCRP, homocysteine, myeloperoxidase and lipoprotein particle size and concentration are being increasingly used to predict cardiovascular diseases in high risk as well as no risk category individuals. This article summarizes the advantages of the above mentioned emerging biomarkers as these circulating biomarkers may be most informative in detecting earlier stages of atherosclerosis before the occurrence of cardiovascular disease.

2. EMERGING BIOMARKERS

2.1 High Sensitivity C - reactive Protein (hs-CRP)

C-reactive protein (CRP) is an acute-phase protein [1] produced by the liver in response to injury or tissue damage. CRP directly binds highly atherogenic oxidized low-density lipoprotein cholesterol (LDL-C) and is present within lipid-laden plaques [1,2], In Atherosclerosis, a chronic inflammatory condition, CRP has been used as a marker for cardiovascular risk. However, conventional CRP assays are not sensitive enough to detect the subtle changes seen in cardiovascular disease. Instead, newer, high sensitivity CRP assays were developed to meet this need). The hsCRP assays can detect CRP at 0.5-10.0 mg/L. This allows for measurement of the CRP protein in patients who would be below the limit of detection [2]. There are large studies showing that hsCRP is in fact elevated in patients who have real cardiovascular risk. (CV) [3,4].

Standard hsCRP assays suffice in settings of active infection, tissue injury, or acute inflammation, which are known to cause marked elevations. CV risk assessment requires a more sensitive assay than the traditional lipid profile, which can accurately detect very low levels of CRP in healthy individuals [5,6].

Some general guidelines for hs-CRP in prediction of risk for CVD are: <1.0 mg/L Low CVD risk, 1.0-3.0 mg/L Average risk for CVD,>3.0 mg/L High risk for future CVD. For hsCRP results that are very high (>10.0 mg/L)

patients should be evaluated for an acute inflammatory condition (one unrelated to CVD) [5].

2.2 Apoproteins

Usually LDL is the primary target for prevention of coronary heart disease (CHD); but other lipoproteins like IDL and VLDL are also supposed to have atherogenic properties and also these particles carry only one apolipoprotein B-100 (Apo B-100). [7] The total Apo B value represents the total number of potentially atherogenic lipoproteins; hence by measuring Apo B we can quantify the amount of all atherogenic or potentially atherogenic lipoproteins that carry this apolipoprotein. Although lipoprotein particles other than LDL can carry Apo B, LDL accounts for the vast majority of Apo B; therefore, it is a good index of LDL particle number. The measurement of apo B is a better estimate of the atherogenic lipoprotein particles than LDL-C concentration, which varies according to the size of LDL [8]. The LDL-C concentration can be normal or even low in obesity, and also in diabetes. The therapeutic goal for apo B in both sexes was 0.9 g/l, which coincides with LDL-C concentration of 3.0 mmol [9].

Reduced levels of Apo A-I, a component of anti-atherogenic cardioprotective HDL, are associated with increased cardiac events. Apo B, Apo A-I and the apo B/apo A-I ratio have been reported as better predictors of cardiovascular events than LDL-C A person with low cardiovascular risk would have low Apo B levels and high Apo A1 levels. If we measure both Apo B and Apo A1 and express them as a ratio of Apo B /ApoA1 we get a powerful cardiovascular risk marker [10,11]. The ratio should be approximately 0.3-0.9. Patients with a higher ratio have elevated Apo B (LDL) and/or low Apo A1 (HDL) and are thus at increased risk. [12,13,14,15] As is already established that LDL, & VLDL particles present an Apo B100 molecule in their structure, hence Apo B100 indicates the total number of potentially atherogenic particles whereas the measurement of Apo A1 represents total antiatherogenicity owing to reverse cholesterol transport by apo A1 [16,17,18,19].

2.3 Lp (a)

Numerous epidiomologic studies have reported a strong correlation between Lp(a) levels and occurrence of atherosclerosis to the extent that it can be classified as the most atherogenic lipoprotein [20]. Lp (a) is a low-density lipoprotein (LDL)-like particle formed by the association of the highly polymorphic glycosylated apolipoprotein (apo (a)) with apolipoprotein B100 (apo B100), the classic protein moiety of LDL. Lp(a) is an LDL particle whose Apo B molecule has formed a disulfide bond with another protein called Apo(a) [20,21].

Serum concentrations of Lp(a) are related to genetic factors; Elevated lipoprotein(a) (Lp [a]) is a genetic risk factor for cardiovascular disease, drugs and diet changes do not typically lower Lp(a) as they do LDL [20]. Concentrations of Lp(a) above 30 mg/dl are associated with increased cardiovascular risk. The risk of having a cardiovascular event increases 2 to 3 fold if Lp(a) cholesterol is > 30 mg/dL [21,22]. Lp (a) interferes with the process of fibrinolysis and may contribute to tissue healing and restoration but also support and accelerate atherothrombotic process hence individuals with both elevated Lp(a) plus LDL cholesterol were at a 10-fold or higher risk of MI [22]. The patient most commonly seen with the Lp(a) abnormality is one with CVD onset approximately one decade earlier than expected, along with a family history of premature CVD or closure of recently placed stents. Unfortunately, this may result in disease in the second or third decade for men and third or fourth decade for women [23].

Lp (a) levels will remain relatively steady throughout life, negating the need for routine monitoring once a patient's levels have been established. The exception is postmenopausal women, in whom Lp(a) levels may increase due to changes in estrogen [24].

2.4 Oxidized LDL

Free radicals occur in biological systems and are produced constantly via metabolic processes. A free radical is an atom or small molecule with unpaired electrons. However, free radicals also have detrimental effects on surrounding cells. oxidation of low-density lipoprotein (LDL) is an early stage of the disease and that oxidized LDL (OxLDL) would contribute to atherogenesis [25,26,27,28,29]. When LDL is co-localized with cells or tissues that are releasing free radicals (such as in an inflamed vessel wall) the free radicals can chemically modify the phospholipids and other components of the lipoprotein [30]. The LDL then becomes oxidized and the modification makes the LDL more atherogenic [31]. Since oxidized LDL is more atherogenic than native LDL it makes sense that oxidized LDL may be a

cardiovascular risk marker some investigators have argued that oxidized LDL measurements give the most accurate snapshot of coronary artery disease (CAD) risk. Oxidized LDL showed a six-fold ability over LDL-cholesterol in predicting disease. If the oxidized LDL/HDL-C ratio is measured, the ability to predict risk is further increased [32] Studies have suggested increased oxidized LDL levels in patients with acute myocardial infarction [33]. Studies in patients who couldn't survive AMI suggests that coronary lesion contained abundant macrophage-derived foam cells with distinct positivity for oxidized LDL and its receptors [34]. These results strongly suggest an important role for oxidized LDL in human coronary atherosclerotic lesions. It has also been reported that oxidized LDL levels are significantly higher in the serum of patients with acute coronary syndrome. Oxidized LDL levels may well become the marker for early diagnosis of acute coronary syndrome [35] While both small and large LDL particles may be atherogenic, it is currently widely believed that small LDL particles are more atherogenic than large particles due to the greater oxidation potential of small particles and their relationship to other metabolic abnormalities, particularly high levels of triglyceride-rich lipoproteins and low serum concentration of HDL cholesterol.

2.5 Lipoprotein-associated phospholipase A2-LpPLA2

Also referred to as platelet-activating factor acetyl hydrolase, is a lipase enzyme found predominantly on the surface of LDL particles.

LpPLA2 is made by inflammatory cells (T cells, mast cells, macrophages) and is then integrated onto the surface of lipoprotein particles. The enzymatic function of LpPLA2 is to hydrolyze oxidized phospholipids resulting in production of lysophosphatidylcholine and oxidized fatty acid [35,36]. The pro inflammatory and atherogenic properties of lysophosphatidylcholine are well known [36].

Blood levels of Lp-PLA2 predict future cardiovascular events in patients with ischemic disease and heart failure. Although LpPLA2 has a positive role in removing oxidized lipids, it also generates inflammatory products in the process. So high levels of LpPLA2 are actually associated with increased cardiovascular risk [35]. Researchers have identified high amounts of LpPLA2 in human atherosclerotic lesions. This association seems to be independent of traditional cardiovascular risk factors [35] Lp-PLA2 testing has been reported to be particularly useful for gauging risk among patients with metabolic syndrome or diabetes [37].

2.6 Sphingolipids

Sphingomyelin (SM) and sphingosine-1-phosphate (Sph-1-P) are proposed to be involved in pathogenesis of atherosclerosis [40]. SM is abundant in atherosclerotic lesions and Sph-1-P is bound to HDL and attributes to the anti-atherosclerotic properties of HDL partly. However, at present, because of difficulty in measuring these sphingolipids more precisely, rapidly, and conveniently, currently sphingolipid measurement are not very common. But it is true that level of sphingolipids can more accurately predict acute coronary syndrome. Moreover, alterations in sphingolipid metabolism contribute to several neurological disorders [38,39]. Because of the well-established role of sphingolipids in altering the calcium homeostasis, sphingolipids may act as future biomarkers for confirmation of atherosclerotic disorders (cardiovascular disease) and several neurological lipid disorders [40,41,42].

2.7 Myeloperoxidase

Myeloperoxidase (MPO), a leukocyte enzyme that promotes oxidation of lipoproteins in atheroma, has been proposed as a possible mediator of atherosclerosis. While a major biological function of MPO is the defense of the organism against infections by generating antimicrobial oxidants, free radicals and other reactive oxidant species [38,39,43] this activity can also lead to oxidative damage of endothelium and vessel wall [44,45]. MPO-derived oxidants impaired the endothelial-protective effect of HDL, leading to endothelial dysfunction [50]. Endothelial dysfunction is associated with the development of atherosclerosis, MPO may contribute to the initiation and propagation of atheromatous plaque, particularly in diabetic patients [46,47]

3. CONCLUSION

Earlier studies and guidelines have emphasized the use of total cholesterol and LDL-C for CVD risk assessment. However, the latest evidence has revealed that after reaching the therapeutic target for LDL-C, a substantial risk for CVD still

remains. Many epidemiological studies have shown that Apo B or Apo B/Apo A-I ratio might be a better predictor for cardiovascular risk than traditional cholesterol measurements [48,49,50, 51,52,53], Measuring Apo B concentration in serum is a better estimate of the number of atherogenic, oxidized LDL particles than LDL-C [54].

When low-density lipoprotein (LDL) becomes smaller and denser, it is more likely to interact with the arterial wall, leading to deposition of cholesterol and initiating or worsening atherosclerosis. Research has shown that high numbers of smaller, denser LDL are more atherogenic than larger, lighter LDL particles. Small, dense LDL particles are associated with more than a three-fold increase in the risk of coronary heart disease [55,56,57,58,59, 60,61,62,63]. This view is supported by findings from epidemiological studies which have shown that individuals with predominantly small LDL particles have greater cardiovascular disease (CVD) risk than those with predominantly large LDL [64,65,66] Though not independently predictive , small dense LDL-C has also been found to be strongly associated with lipoprotein-associated phospholipase A2 activity and hs-CRP, Apo B. MPO and classical lipid profile meausrements [47,67,68,69,70]. Role of small dense LDL –C in predicting CAD has also been reported by studies conducted earlier in type 2 diabetic patients where treatment with fenobrate greatly reduces the progression of CAD by increasing the LDL particle size and also the Apo B concentrations, while low LDL-C or ApoB levels, a preponderance of small, dense LDL particles increased the progression of coronary atherosclerosis [71]. MPO causes modification of Apo A-I in HDL, impairing reverse cholesterol transport [71,72].

Hyperhomocysteinemia might also contribute to atherogenesis and thrombosis because homocysteine is known to oxidize LDL, and also convert it (LDL) to its thiolated form which is taken up by foam cells much faster [65], Independently, homocysteine reduces bioavailability of nitric oxide (NO) and causes deterioration of the elastic structure of the arterial wall [72,73,74,75].

These markers can be considered to be potential emerging markers to predict a CAD and also be the future targets for avoiding or reducing/ delaying the progression of CAD.

COMPETING INTERESTS

Authors have declared that no competing interests exist

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