A brief review of biomarkers for preventing and treating cardiovascular diseases

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ABSTRACT

Cardiovascular diseases are the most prominent circulation disorders around the world. Biomarkers are characteristic biological properties that can be objectively measured as an indicator to evaluate a variety of health or disease characteristics. Cardiac biomarkers are a valuable tool for assessing the pathogenesis and diagnosis of cardiovascular diseases. In this review, we will focus on the major biomarkers used in recent clinical research for the diagnosis of cardiovascular diseases, which include mean platelet volume, hyperhomocysteinemia, serum magnesium, microalbuminuria, and prolongation of QT interval and dispersion. We also highlight the key findings of clinical case report based studies presented in this issue of JCDR.

Key words: Biomarkers, cardiovascular diseases, pathogenesis

Cardiovascular diseases are heterogeneous circulation disorders that include rheumatic, hypertensive, ischemic, cerebrovascular, and inflammatory heart diseases, based on the World Health Organization's classification. In 2008, there were an estimated 57 million global deaths, of which 30.5% were attributed tocardiovascular disease.[1] This fraction is greater than the proportion of combined deaths stemming from other diseases such as malignant neoplasms, other neoplasms, diabetes mellitus, nutritional/endocrine disorders, respiratory diseases, and digestive diseases. Death from cardiovascular diseases is preventable with accurate early-stage diagnosis and subsequent proper treatment. Correct diagnosis is dependent upon cardiac biomarkers, the focus of this issue of JCDR. We are pleased to present a review, four clinical case report-based studies and ten clinical/translational research articles that are relevant to use of biomarkers for early prevention and therapeutic targets. In this review, we will discuss these major biomarkers and highlight recent clinical case report based studies. JCDR is dedicated to publishing recent clinical case report based studies and up-to-date biomarkers in clinical and basic cardiovascular research, and welcomes submissions that add to our growing body of knowledge on the pathogenesis of cardiovascular disease.

Access this article online	
Quick Response Code:	Website: www.jcdronline.com
	DOI: 10.4103/0975-3583.102688

Cardiovascular diseases are usually diagnosed in middle-aged or elderly individuals regardless of gender. The underlying pathogenesis of cardiovascular diseases is atherosclerosis. The leading pathological process of atherosclerosis, however, begins asymptomatically early in life and progresses gradually through adolescence and early adulthood.[2,3] Despite continuous improvement in preventing and treating cardiovascular diseases, subclinical atherosclerosis in an asymptomatic population has long been overlooked. This leads to the loss of critical windows for prevention and to long-term delay between the initial development of atherosclerosis in young individuals and

the sudden and fatal manifestation of heart disease several decades later. Therefore, it becomes urgent to identify reliable risk factors/biomarkers forprevention, early detection and treatment of the diseases. Histopathological and biological alterations during atherosclerosis have been utilized to provide insight into cardiovascular disease progression. Dr. Thej and colleagues at Sri Devaraj Urs Medical College uncovered histomorphological atherosclerotic alterations in 113 deceased individuals whose ages ranged from 8 to 85 years old.[4] They observed an alarming trend of increased death with intermediate lesions in young individuals of 15–34 years old. Their study also revealed that males are twice more likely to die from cardiovascular disease as compared to females. Interestingly, the artery location is associated with onset of atherosclerosis. For instance, atherosclerotic lesions at the left anterior descending artery were more frequently observed compared to other coronary arteries. This report highlights the importance of diagnosing early onset of cardiovascular diseases for prevention and treatment, especially in asymptomatic individuals.

Much data have accumulated to support the use of certain risk factors and biomarkers as valuable tools for preventing and treating cardiovascular diseases. In the second original clinical research article, Dr. Vitthal *et al.* at SDM College of Medical Sciences in India identified mean platelet volume (MPV) as a reliable biomarker for cardiovascular diseases.[5] They reported that patients suffering from acute myocardial infarction (MI, 39 subjects) and stable coronary artery diseases (CAD, 24 subjects) displayed higher MPVas compared to 65 healthy controls. They concluded that elevated MPV can be used as a biomarker for monitoring risk of acute MI and CAD. Consistently, previous studies reported that increased MPV was associated with risk for cardiovascular disease in the elderly population.[6] Importantly, an increased MPV also indicates a poor outcome among survivors of MI[7] suggesting that MPV may be a potential therapeutic target.[8,9]

Homocysteine, a homologue of cysteine, is synthesized from methionine by removal of its terminal C^{ε} methyl group. It was suggested to be a modest independent predictor of coronary heart disease.[10,11] Dr. Naghshtabrizi and coworkers at Hamedan Medical University in Iran found an association between cardiovascular disease and elevated serum homocysteine or the homozygous C677T mutation in methylene tetrahydrofolate reductase,[12] a gene that encodes an important enzyme in homocysteine metabolism. Increased plasma homocysteine results from multiple factors, such as vitamin deficiencies (B6, B9, and B12), renal impairment, and gene polymorphisms. However, it remains debatable whether lowering homocysteine through supplementing vitamin B6, B9, and B12 prevents cardiovascular disease.[13,14]

Serum magnesium is another biomarker for cardiovascular disease, according to areport from Dr. Mahalle's group at Deenanath Mangeshkar Hospital and Research Center in India.[15] They detected elevated total cholesterol, triglycerides, very low-density lipoprotein (VLDL) and LDL and reduced high DL cholesterol in subjects with lower serum magnesium (<1.6 mg/dl) and CAD compared to controls. Diabetes, dyslipidemia, and hypertension were negatively correlated with serum magnesium levels. Furthermore, dietary magnesium was positively correlated with serum magnesium. The authors concluded that hypomagnesaemia and low dietary magnesium in CAD patients are strong risk factors. Magnesium behaves like a natural calcium channel blocker to attenuate blood pressure and blood pressure-induced CAD.[16,17] Supplementing dietary magnesium may improve hypertension and CAD.

Microalbuminuria (MA) is a persistent, increased urinary excretion of albumin,[18] and based on the findings of Dr. Goud and colleagues at RAK Medical & Health Sciences University in United Arab Emirates,[19] may also be a candidate biomarker for cardiovascular disease risk. They found increased circulating levels of MA, high-sensitivity C-reactive protein (hsCRP), and LDL cholesterol in MI patients as compared to healthy individuals. The authors concluded that MA and hsCRP evaluation may improve cardiovascular risk prediction when combined with traditional lipid profiles. Similarly, other researchers reported that MA also correlates with various cardiac abnormalities and diseases, such as left ventricular dysfunction and hypertrophy, electrocardiographic abnormalities, and ischemic heart disease.[20] Strategies to reduce MA are recommended to delay progression of cardiovascular diseases. Perhaps the most important and efficient approach is the reduction of blood pressure. Angiotensin receptor blocker used alone or in conjunction with an ACE inhibitor may facilitate a reduction in MA.[21] Thiazide diuretics function to decrease proteinuria,[22] and dietary salt restriction may also promote reduction of urinary albumin excretion.[23]

Dr. Akintunde and colleagues at Ladoke Akintola University of Technology in Nigeria reported that QT interval and dispersion may be a risk factor for hypertension.[24] QTmax, QTcmax, QTd, and QTcd were higher in hypertensive subjects compared to controls. QTc dispersion was 36.4% greater in hypertensive subjects. Hypertensive subjects with aberrant QT had higher mean waist hip ratio, mean body

mass index, and higher prevalence of smoking compared to controls. Moreover, QT prolongation and increased QTc dispersion are common among newly diagnosed hypertensive individuals. The authors concluded that therapies targeting both hypertension and obesity are important for newly diagnosed hypertensive patients. Studies have demonstrated the relationship between mortality and prolonged QT interval and increased QT interval dispersion in cardiovascular diseases.[25] Prolongation of the QT interval or QTc may reflect the presence of ischemic heart diseases,[26] and increased QT interval dispersion may mirror discrepant repolarization characteristics of different areas of the heart.[27]

Hypertension is associated with obesity or metabolic syndrome. Dr. Lemboa's group at National University of Cuyo in Argentina investigated vascular impairment in metabolic syndrome using a rat model.[28] They chronically administrated fructose to spontaneously hypertensive rats (FFHR) to generate impairment in vascular repairing by endothelial progenitor cells (EPC). Decreased proliferation of EPC and colony forming units were found in both fructose-treated FFHR (SHR fructose feed rats) and FFR (WKY fructose feed rats) compared to untreated controls. The fructose-fed groups also showed increased apoptotic (annexinV^+/7AAD^{dim}) EPC, which was reversed after fructose feeding was terminated. The authors suggested that increased EPC apoptosis could lead to impaired vascular repair.

Rhabdomyolysis is an uncommon but life-threatening adverse effect of simvastatin therapy. Dr. Alreja and coworkers at School of Medicine at Tufts University in MA in the United States reported a clinical case of rhabdomyolysis in a 73-year-old male caused by an unusual interaction between azithromycin and simvastatin.[29] The patient presented with weakness of extremities and a significant increase in creatinine phosphokinase levels and acute kidney injury. Simvastatin therapy was concluded and supportive therapy with intravenous saline and bicarbonate was initiated. The serum creatinine and creatine phosphokinase returned to baseline over the next 7 days. Two months later, simvastatin was resumed without any recurrence of symptoms.

Dr. Patra and colleagues at Department of Cardiology at Sri Jayadeva Institute of Cardiovascular Sciences and Research in India presented a clinical case report based study of a patient of Ebstein's anomaly associated with biventricular noncompaction presented with Wolf Parkinson White syndrome (WPWS).[30] A 34-year-old male patient presented with recurrent attack of palpitation and chest pain due to WPWS. Two-dimensional echocardiography demonstrated features of Ebstein's anomaly along with biventricular noncompaction. Color flow Doppler studies confirmed the presence of blood flow within the trabeculations. Biventricular myocardial noncompaction associated with Ebstein's anomaly, presented with WPWS is a very rare association. The patient was treated with radiofrequency ablation of right sided posteroseptal accessory pathway of WPWS and was asymptomatic in further follow-up. Dilated cardiomyopathy (DCM) is the third most common cause of heart failure and the most frequent cause of heart transplantation with an estimated prevalence of 1:2500. Dr. Seemann and coworkers at Henri Mondor Hospital in France presented a clinical case report based study of severe dilated cardiomyopathy with left ventricular apical thrombus in a 48-year-old patient.[31] The patient's medical history included diabetes mellitus and hypertension. In this case, the authors further discussed the criteria for diagnosis and therapy.

In summary, this editorial review provides a concise overview of the diverse array of reportsin the current issue that encompass the use ofbiomarkers for preventing and treating cardiovascular diseases. Lastly, we would like to express our sincere appreciation to the authors for their contribution and to reviewers and editorial staff for their dedication and hard work, propelling the *JCDR* into one of the most prestigious journals in the field of cardiovascular research.

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How to cite this article: Sun X, Jia Z. A brief review of biomarkers for preventing and treating cardiovascular diseases. J Cardiovasc Dis Res 2012;3:251-4.

Source of Support: Nil, **Conflict of Interest:** None declared.