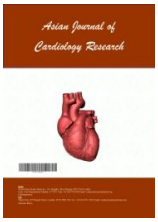

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Multi-Biomarker-Based Risk Assessment Model: Implications in Patients with Hypertensive Heart Disease

Nelson I. Oguanobi[1*]

[1]Department of Medicine, University of Nigeria Teaching Hospital Enugu, Nigeria.

Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

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Review Article

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ABSTRACT

Systemic hypertension is a leading cause of morbidity and mortality worldwide. Primary and secondary prevention of cardiovascular adverse events are limited by the generally poor predictive value of traditional risk factors assessment models. The use of tissue-specific cardiac biomarkers that can reliably assess pathologic conditions is important for early detection and prevention of target organ damage. This review article highlights the role of multi-biomarker models in providing insight to greater understanding of the pathophysiological mechanisms and their implications on cardiovascular morbidity in systemic hypertension.

Keywords: Heart; multi-biomarkers; hypertension; implications; cardiovascular.

1. INTRODUCTION

Hypertension is the most important contributor to morbidity and mortality worldwide constituting a major risk factor for coronary artery disease, arrhythmias, heart failure, cerebrovascular disease, peripheral artery disease, retinopathy and renal failure [1,2]. Assessing the risk for cardiovascular disease is an important aspect in critical clinical decision making in the management of hypertension [3]. These risk factors are traditionally categorized as modifiable

**Corresponding author: Email: nelson.oguanobi@unn.edu.ng, nelifyik@yahoo.com, nelsonoguanobi@gmail.com;*

and non-modifiable risk factors.

Modifiable risk factors include unhealthy diets (excessive salt intake, a diet high in saturated fat and trans fats, low intake of fruits and vegetables), sedentary lifestyle, obesity, tobacco and alcohol consumption. Non-modifiable risk factors include a family history of hypertension, age greater than 65 years and presence of co-morbidities such as diabetes or kidney disease [3]. According to the Framingham study, high levels of triglycerides and low high density lipoprotein (HDL) cholesterol increase the cardiovascular risk level [4,5]. Statistical models that incorporate a number of risk factors thereby producing more consistent results have been proposed to improve the accuracy of clinical judgment [6,7,8].

2. BIOMARKERS AND HYPERTENSION

Clinical risk assessment remains the keystone in the management of patients with hypertension. However, clinical assessment is generally limited by lack of consistency especially with less experienced clinicians [9,10,11]. The identification of circulating and tissue specific risk markers for cardiovascular disease has significant potential to improve patients' management and in the identification of high risk individuals for preventative strategies.

The pathophysiology of hypertension involves the interaction of multi-factorial mechanisms and the disease outcome and prognosis varies among individuals and racial groups [12,13,14].

Notable mechanisms involved in the pathogenesis of hypertension include abnormalities of renal sodium handling, neurohormonal and adrenergic overactivity, endothelial and vascular dysfunction, reduced fibrinolytic potential, enhanced inflammatory and oxidative stress [12,13,14,15].

These intricate mechanisms are responsible for the structural remodeling of the myocardium and blood vessels leading to multiple target organ damage [16,17]. The facilitation of these adverse events in hypertensive patients constitute part of the spectrum of cardiovascular continuum, which represents a holistic view of the sequence of events connecting cardiovascular-related risk factors with the progressive development of pathological-related tissue remodeling [18].

Left ventricular hypertrophy is the first compensatory mechanism of the myocardium in response to hypertension-induced pressure overload [19]. Hypertensive heart disease is defined by the presence of left ventricular hypertrophy in the absence of a cause other than arterial hypertension [20,21]. It is considered as one of the most common aetiological conditions predisposing to ischaemic heart disease and heart failure [22,23,24,25].

Left ventricular hypertrophy results from growth of cardiomyocytes in response to both mechanical stretch and activation of humoral growth factors such as Cardiotrophin-1 (CT-1), metalloproteinases 1 and angiotensin II [26,27,28,29,30].

Similar pathologic changes in the vascular tissues mediated by multiple biomarkers including E-selectin, fibrinogen, C-reactive protein (CRP) and plasma vascular endothelial growth factor (plasma VEGF), result in endothelia dysfunction, vascular stiffness and atherosclerosis [31,32,33,34]. These pathological processes are responsible for hypertension-associated vasculopathy in the coronary, retinal, renal and cerebral vasculatures [25,34].

The primary prevention of cardiovascular disease relies on the ability to identify at-risk individuals long before the development of overt events.

Interestingly, biomarkers capable of detecting specific earlier stages of the cardiovascular continuum such as increased levels of urinary albumin excretion (UAE), plasminogen activator inhibitor-1 (PAI-1), asymmetric dimethylarginin (ADMA), symmetric dimethylarginin (SDMA), Myeloperoxidase and F2-isoprostanes have been identified [3,18,35,36].

One potential way of addressing the multi-factorial aetiologic characteristics of hypertension is the utilization of a multi-biomarker approach for short-term and long-term stratification as well as prognostication of patients.

Data derived from cross sectional and longitudinal studies on cardiac biomarkers in hypertension have demonstrated that biomarkers representative of key biological pathways, such as C-reactive protein ([CRP] marker of inflammation) and aldosterone (neurohormonal activity), are elevated before the onset of overt hypertension [37,38,39].

3. COMPONENTS OF MULTI-BIOMARKER PANEL

Biomarkers provide a powerful approach to understanding the spectrum of cardiovascular disease with a wide range of applications. A typical multi-biomarker panel consists of the following:

3.1 Markers of Aetiopathogenesis:

(a) Vascular dysfunction and neurohormonal activation: plasma rennin, norepinephrine, angiotensin-II, Arginine vasopressin, urine creatinine/albumin ratio, plasma aldosterone, plasma vascular endothelial growth factor (plasma VEGF).
(b) Inflammatory and oxidative stress: C-Reactive proteins-HS, P-selectin, serum uric acid, Tumor necrosis factor alpha, interlukin-6, ratio of blood neutrophils/lymphocytes, red blood cell distribution width.

3.2 Markers of Disease Progression

Troponin T and I, Microalbuminuria, e-GFR, plasminogen activator-1 (PAI-1) antigen.

3.3 Markers of Target Organ Damage

(a) Myocardiac stretch: N-terminal pro B-type natriuretic peptide (NT-Pro-BNP), atrial natriuretic peptide (ANP), creatine kinase-MB(CK-MB), lactate dehydrogenase, plasma homocystein, myoglobulin and myeloperoxidase.
(b) Matrix remodeling: Cardiac matrix metalloprotinases, Collaginase pro-peptidees, tissue inhibitors of metalloproteinases-1,
(c) Myocardial injury: CK-MB, Troponin-T, Troponin-I, Heart-type fatty acid binding protein, Pentraxin-3, heart shock protein-60,

4. POTENTIAL IMPACT OF CARDIOVASCULAR MULTI-BIOMARKERS

An important role of the multi-biomarker approach is in the elucidation of the link between risk factors and disease outcome in hypertension. Target organs complications of hypertension are known to vary between individuals [3]. While some patients present with predominantly cardiac, renal or neurological complications in isolation, others have multiple organ complications. The reason for this differential outcome is largely unknown.

Genome-wide linkage analyses have identified loci linked to genes influencing blood pressure levels as well as genes that contribute to development of hypertension-related target-organ diseases [40]. Consequently, biomarker studies may provide further insight. In this regard, prognostic biomarker can provides information on the likely course of a disease condition in an untreated individual or in an individual treated with conventional therapies.

Secondly, individual genetic variations exist in the structures and quantity of proteins associated with the various pharmacokinetic and pharmacodynamic mechanisms involved in drug handling and therapeutic response. Treatment selection that is tailored to patients' needs could be enhanced by the use of predictive biomarkers. There is increasing interest in identifying genes that influence the pharmacodynamic determinants of blood pressure response [41,42,43]. The pathophysiological changes in the target organs in response to therapy can be assessed with pharmacodynamic biomarkers. A good example is the exploration of the effects of antihypertensive drugs in reversing cardiac remodeling due to hypertension. A genetic biomarker study by Cursi et al demonstrated the role of α-adducin gene polymorphism in identifying a subset of salt-sensitive hypertensive patients more responsive to diuretic therapy [44].

An efficient and reliable multi-marker panel for evaluation of hypertension risk factors would include biomarkers that are representative of each pathophysiological pathway. Wang et al, evaluated the usefulness of 10 biomarkers for predicting death and major cardiovascular events in approximately 3000 persons followed for up to 10 years [45]. They measured high-sensitivity C-reactive protein (a marker of inflammation); B-type natriuretic peptide, N-terminal pro–atrial natriuretic peptide, serum aldosterone, and plasma renin (markers of neurohormonal activity); fibrinogen (a marker of thrombosis and inflammation); plasminogen-activator inhibitor type 1 (a marker of fibrinolytic potential and endothelial function); d-dimer (a marker of thrombosis); homocysteine (a marker of endothelial function and oxidant stress); and the urinary albumin-to-creatinine ratio (a marker of glomerular endothelial function). Biomarkers from multiple, biologically distinct pathways were found to be associated with increased risks of

death and major cardiovascular events.

Several other studies have reported similar findings corroborating the evidence that combining biomarkers increases the accuracy and predictive value of cardiovascular risk assessment in hypertension [9,46,47]. However, the optimal combinations for diagnosis or prognosis need to be defined. In addition, the inherent correlation among measured biomarkers needs to be taken into consideration. Furthermore, the attendant high cost, inadequate requisite technical facilities and expertise in many countries may momentarily limit their usefulness.

5. CONCLUSION

Elucidation of the large variations in individual and genetic susceptibility to target organ damage in hypertension has been a subject of keen research interest. Assessment of individual circulating cardio-biomarkers in conjunction with the standard traditional risk factors has significantly improved cardiovascular disease risk prediction. The use of multi-biomarker models provides brighter prospect for further understanding of the pathophysiological mechanisms and their implications on cardiovascular morbidity in systemic hypertension.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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