

Markers in Hypertension: Insights for an Enhanced Blood Pressure Management

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Received date: July 02, 2014; Accepted date: July 21, 2014; Published date: August 03, 2014

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Abstract

Background and objectives: Hypertension is a prevalent condition that represents a significant morbidity and mortality. In this review, we sought to highlight the value of markers in systemic hypertension.

Design and method: we conducted a mini-review focusing on markers in hypertension, also we reviewed the JNC8-2014 and ESC/ESH-2013 recommendations in this perspective; a Pubmed search was performed accordingly.

Results: we presented and discussed markers of diagnosis and physiopathology of hypertension, markers of target organ damage and markers of blood pressure progression, with a focus on biomarkers. Genetics of hypertension is a rapidly moving field and at least 38 foci correlated to blood pressure are currently identified; the Ras homologous (Rho; RhoA, Rac1) are mainly involved in vascular smooth muscle tonus and vasoactivity; adipokines (leptin, TNF- α , IL-6, MCP-1, and IL-1) expression is marked in patients with obesity related hypertension. The baroreceptor is a marker of dysautonomia which is implicated in the pathogenesis of hypertension; miR-9 and miR-126 are markers of target organ damage in hypertensive patients. Markers of endothelial dysfunction, systemic inflammation, and oxidative stress were also discussed as causative or target organ markers in this context, with a focus on C-reactive protein and nitric oxide.

Conclusion: markers, mainly biomarkers, play an increasingly critical role in hypertension evaluation and management.

Keywords: Hypertension; Markers; Management; Morbidity; Mortality

Introduction

Hypertension (HTN) is the most prevalent chronic medical condition seen in primary care and it is a major risk factor for cardiovascular morbidity and mortality [1]; given the damaging effects of HTN on many organs, including the heart, arteries, brain, eyes, and kidneys, HTN is considered a major global health burden. The prevalence of HTN appears to be around 30–45% of the general population, with a sharp increase with ageing [2]. The physiopathology of HTN is multi-factorial involving mainly the autonomic nervous system and the renin-angiotensin axis and the underlying mechanism of HTN is often heterogeneous, polygenic and multi-factorial in nature [3,4].

HTN has many clinical patterns and/or etiopathological forms: essential HTN, secondary HTN, white-coat HTN, isolated systolic HTN, masked HTN, pulmonary HTN, pregnancy related HTN. Markers in HTN can be defined as any clinical or paraclinical parameter or index that may provide additional information regarding diagnosis, consequence and progression of HTN. Herein we present a review discussing the value of markers in HTN, with a focus on biomarkers, while restraining to systemic HTN in the adults.

Background

Classical diagnosis of HTN is mainly based on clinical or office measurement, though ambulatory blood pressure monitoring may be required in grey cases or when specific parameters regarding HTN profile and trend are required. Adequate blood pressure control is primarily based on a comprehensive understanding of the etiopathology of HTN, and such understanding must be individualized given the great variability and multifactorial nature of the disease; herein, markers may help to clarify the physiopathology of HTN and accordingly to administer tailored management. Of note, a significant proportion of hypertensive patients have uncontrolled blood pressure, and this may be related to undiagnosed HTN, inappropriate management, resistant form of HTN and/or to poor patient compliance [5].

Endothelial function plays a significant role in maintaining vascular tone and endothelial dysfunction is one of the early changes found in atherosclerosis, yielding defective vasomotor response involved in the genesis of HTN. A significant proportion of hypertensive patients are diagnosed at an advanced stage of the disease, also the percentage of undiagnosed HTN is estimated high in the general population given the “silent” nature of the condition in most cases [2]. Accordingly, many cases of HTN are diagnosed when target organ damage has already started, and markers of progression and target organ damage may give valuable clues regarding severity and expected duration of a previously undiagnosed HTN.

Methods

A Pubmed search was performed, with “hypertension”, “biomarkers” and “markers” introduced as search parameters, also JNC8-2014 and ESC/ESH-2013 along with their relevant references were reviewed. A total of 121 articles were reviewed, among these only 33 articles were found relevant and were considered for this study.

Markers

This section was divided into 3 subsections, addressing (1) the value of markers in diagnosis, etiology and genetics of HTN, (2) markers of target organ damage and (3) markers of HTN progression and control.

Markers of diagnosis, genetics and physiopathology

It is well established that HTN is determined by both genetic and environmental factors and their complex interactions; the control of arterial pressure is a complex interaction of hormones, local vascular factors, and neural mechanisms. The overactivity of the sympathetic nervous system plays an important role in the development of HTN [6]. One of the direct markers of sympathetic hyperactivity in the heart rate: Lonn et al. showed that resting and 24-hour-average heart rates are independently associated with a significant increase in cardiovascular morbidities including HTN [7].

Recent meta-analyses have successfully identified at least 38 loci that have crucial involvement in the pathogenesis of HTN [8]. Moreover, plasma cyclophilin-A is recognized as a novel biomarker for untreated HTN, and it is valuable in the early pathogenesis of essential HTN [9]; similarly, high circulating levels of angiotensin converting enzyme mRNA are correlated with the development of essential HTN [10].

Vascular tone plays a major role in the regulation of blood pressure, and increased vascular tone is often encountered in essential HTN. In humans, Ras homologous (Rho; RhoA, Rac1, and Cdc42) have a main function in the regulation of the actin cytoskeleton; more specifically, RhoA and Rac1 have been identified as key signaling molecules playing important roles in several different steps of blood pressure regulatory processes. RhoA negatively regulates nitric oxide production whereas Rac1 has the opposite effect enhancing nitric oxide activity and expression [11]. Consequently, there is an antagonistic effect of Rac1 and RhoA on vascular smooth muscle cells yielding opposite roles in arterial tone regulation and a depletion of Rac1 signaling in vascular smooth muscle cells plays a critical role in the pathogenesis of HTN [12].

Metabolomics is a relatively new field of research used to evaluate metabolic perturbations associated with disease and to identify disease biomarkers; more specifically, this new field has been increasingly used to characterize risk factors for HTN [3]. Obesity is strongly associated with many cardiovascular diseases, mainly HTN. In this context, several phenomena are involved in the development and maintenance of HTN, including activation of the sympathetic nervous system, the renin-angiotensin system, endothelial dysfunction and renal functional abnormalities [13]. Adipose tissue produces several molecules such as leptin, resistin, adiponectin, as well as cytokines such as TNF- α , IL-6, MCP-1, and IL-1. The secretion of such adipokines is stimulated via the intracellular signaling pathways in the adipose tissue, mainly mediated by inflammation and oxidative stress, and these adipokines interact with the microvascular endothelium and

vasoactivity; herein, it is already established that high level of serum leptin is associated with higher levels of blood pressure [14,15].

The baroreceptor function is to keep blood pressure close to a particular set point over a relatively short period of time; the ability of the baroreflex to buffer acute changes in blood pressure is well established and its role in long-term control of blood pressure is less well established [6]. Any condition that impedes baroreflex function contributes to hemodynamic dysregulation, such conditions include atherosclerosis and endothelial dysfunction. Accordingly, a dysfunction of the baroreflex is considered a marker of HTN, and many parameters allow evaluation of baroreflex function like heart rate turbulence and heart rate variability [6].

Arterial stiffness is a direct consequence of arterial remodelling in HTN, also aortic pulse wave velocity and carotid distensibility are directed correlated with increased arterial stiffness, namely in isolated systolic HTN [16]. Secondary forms of HTN, such as primary hyperaldosteronism, Cushing's syndrome, pheochromocytoma, and renal artery stenosis etc, have specific markers for diagnosis such as plasma metanephrine measurements, plasma aldosterone level, and vanilylmandelic acid [17]; moreover, the role of imaging is essential to rule out renal artery or kidney parenchymal disease. Of note, some of these conditions have an established genetic basis like aldosterone producing adenomas where somatic mutations in the KCNJ5, ATP1A1, ATP2B3 or CACNA1D genes are present in more than half of cases [18].

Markers of target organ damage

Micro RNA (miR-9 and miR-126) is closely related to essential HTN in humans, also they were found associated with clinical prognostic indices of hypertensive target-organ damage [19]. HTN is the main cause of heart failure with preserved systolic function and echocardiography provides specific clues in HTN: besides left ventricular hypertrophy, the early mitral velocity/basal tissue velocity ratio (E/E') constitutes a valuable marker of diastolic dysfunction and left ventricular filling pressure, reflecting target organ (myocardial) damage in this setting [20]. Moreover, higher concentrations of procollagen-III-N-terminal peptide are associated with diastolic dysfunction, myocardial fibrosis and aortic stiffness in HTN [21,16].

The value of C-reactive protein (CRP) as a biomarker in HTN is considerable, CRP levels associate with vascular stiffness, atherosclerosis and the development of end-organ damage; moreover, high CRP levels in normotensive patients have been shown in multiple cohorts to foretell the development of HTN on follow-up. Several experimental studies have unraveled an active implication of CRP in the development of endothelial dysfunction and vascular stiffness independently of the value of blood pressure in HTN [22,23]. The involvement of genetic factors that predict CRP values independently of environmental factors is controversial.

Increase in pulse pressure and pulse wave velocity was found associated with higher level of brain natriuretic peptide (BNP) along with (micro)albuminuria; this finding suggests that altered central hemodynamics causes simultaneous damage/dysfunction in the heart and kidney, which could then contribute to cardiorenal syndrome in HTN [24].

Endothelial function is established as etiopathological factor of HTN and biomarkers of endothelial dysfunction (von Willebrand factor, intercellular adhesion molecule 1 and oxidized low-density lipoprotein) are found higher in patients with HTN related to primary

hyperaldosteronism; endothelial dysfunction in this setting may be considered as marker of target organ damage rather than a causal factor [25]. Endocan, also called ESM-1 (endothelial cell specific molecule-1) is a biomarker of neoangiogenesis and endothelial dysfunction in diseases such as cancer, hypertension and sepsis, and it may be used to monitor endothelial dysfunction reversal in HTN [25,26]

Markers of hypertension progression and control

Significant involvement of endothelial dysfunction, systemic inflammation, and oxidative stress in the development of HTN is already established; accordingly, biomarkers reflecting the expression of these phenomena such as IL-6, TNF- α and CRP are found in higher concentrations in patients with HTN when compared to normotensive people [26].

Interestingly, blood pressure control was found to reverse endothelial dysfunction in HTN: blood nitric oxide increased, plasminogen activator inhibitor 1 (PAI-1) and CRP levels decreased, also flow mediated vasodilatation improved; of note, such improvements were independent of the type of anti-hypertensive medication used [27].

Non-dipper HTN is established as additive risk factor and carries a worse prognosis compared to dipper HTN. Chemerin is a novel adipokine that plays a role in inflammation and atherosclerosis; Meric et al. [28] reported that chemerin is higher in non-dippers compared to dippers and normotensives; similarly, Çaylı et al. found that elevated serum concentration of high-sensitivity cardiac troponin T (hs-cTnT), even when it is within normal range, is an independent predictor of non-dipper HTN [29].

Oxidative stress is involved in the pathogenesis of HTN, also it has significant role in the development of arterial wall remodelling and stiffness [30]. Redox imbalance triggers the activity of a number of

signalling pathways mediated by reactive oxygen species (ROSs) and reactive nitrogen species (RNSs) [31]. Biomarkers of oxidative stress such as asymmetric dimethylarginin (ADMA), symmetric dimethylarginin (SDMA), advanced oxidation protein products (AOPP) and oxidised low density lipoproteins (ox-LDL) are typically higher in patients with uncontrolled HTN [30].

Biomarkers of acute HTN crisis

Most cases of hypertensive crisis occur on the background of sustained chronic HTN with paroxysmal peaks related to psychoneuroendocrine mechanism, where psychological stress plays a major role. Serum levels of cortisol and norepinephrine metabolites are reported higher during hypertensive crisis in patients with mood disturbance and anxiety when compared to hypertensive patients with “normal” mood profile [26].

Clinical implications

HTN genetics is a rapidly moving field that is unfolding the mechanisms of blood pressure heritability and physiopathology; hence it may allow future translation of genetic findings to HTN treatment and prevention. Obesity is established as important co-morbidity in HTN, adipokines secreted in adipose tissue worsen endothelial dysfunction, and therefore obesity prevention and control are essential in blood pressure control. The continuing discovery of mechanisms regulating appetite and metabolism is expected to lead to new therapies for obesity-induced HTN. Pharmacogenetics and pharmacogenomics bring closer a perspective of individualized approach to HTN, and such innovative approaches may give insights into blood pressure control and possibly cure of HTN [32,33]. Table 1 shows a summary of the main markers discussed in this paper along with their relevant clinical values.

Markers	Markers	Value
Diagnosis, genetics and phyiopathology	Resting heart rate	Increased sympathetic activity
	Average 24-hour heart rate	Increased sympathetic activity
	Cyclophilin-A	Uncontrolled HTN
	Rac1 and RhoA	Endothelial dysfunction
	Leptin	Inflammation and oxidative stress
	TNF-alpha, IL-1, IL-6	Inflammation and oxidative stress
	Baroreceptor function	Acute blood pressure control
	Aortic pulse velocity	Arterial stiffness
	metanephrines levels	Pheochromocytoma
	Serum cortisol	Cushing syndrome
	Aldosterone levels	Hyperaldosteronism
Target organ damage	KSNJ5, ATPA1, ATP2B3, CACNA1D	Aldosterone secreting adenoma
	miR-9 and miR-126	target organ damage
	E/E' (tissue Doppler)	Diastolic dysfunction
	Procollagen-III	Myocardial fibrosis

	C reactive protein (CRP)	Inflammation, atherosclerosis, Endothelial dysfunction
	Brain natriuretic peptide (BNP)	Hemodynamic dysfunction
	(micro) albuminuria	Renal damage
	Ox-LDL	Endothelial dysfunction
	Endocan	neoangiogenesis
HTN progression and control	CRP, TNF-alpha, CRP	Oxidative stress, inflammation, endothelial dysfunction
	Nitric oxide increase, PAI-1 and CRP decrease	Reversal of hypertension , endothelial dysfunction
	Chimerin	Non-dipper HTN
	ADMA, SDMA, ox-LDL, AOPP	Oxidative stress

Table 1: Table showing different markers with their potential relevant clinical value

Conclusion

Genetics and metabolomics of HTN are promising fields for understanding and managing HTN. Blood pressure management must aim to decrease related morbidity and mortality, beyond controlling blood pressure levels. The Ras homologous, adipokines, baroreceptor activity, CRP, redox imbalance, endothelial function, E/E', plasma Cyclophilin-A, etc. are essential markers to be evaluated in HTN. Whether for diagnosing genetic basis or evaluating target organ damage or progression of HTN, such markers represent clues for a better blood pressure control with concomitant decrease in morbidity and mortality.

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