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MINIREVIEWS

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ABOUT COVER

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AIMS AND SCOPE

The primary aim of *World Journal of Hypertension* (*WJH*, *World J Hypertens*) is to provide scholars and readers from various fields of hypertension with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJH mainly publishes articles reporting research results and findings obtained in the field of hypertension and covering a wide range of topics including atherosclerosis, atrial fibrillation, blood pressure measurement, cerebrovascular diseases, endocrine hypertension, experimental hypertension, hemodynamics, imaging procedures, malignant hypertension, pregnancy-induced hypertension, renal hypertension, renovascular hypertension, hypertension-related heart failure, hypertensive retinopathy, masked hypertension, microcirculation, renin-angiotensin system, and white coat hypertension.

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MINIREVIEWS

Cardiac markers: Role in the pathogenesis of arterial hypertension

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Abstract

Cardiac biomarkers may play unique roles in the prognostic evaluation of patients with hypertension, as many cardiac biomarker levels become abnormal long before the onset of obvious cardiovascular disease (CVD). There are numerous cardiac markers. However, this review article only reported the roles of creatinine kinase-MB, cardiac troponins, lipoprotein a, osteopontin, cardiac extracellular matrix, C-reactive protein, cardiac matrix metalloproteinases, cardiac natriuretic peptides, myoglobin, renin, and dynorphin in the pathogenesis of hypertension. This article explained recent major advances, as well as discoveries, significant gaps, and current debates and outlined possible directions for future research. Further studies are required to determine the association between myoglobin and other cardiac markers in hypertension. Moreover, therapeutic approaches are required to determine the early control of these cardiac markers, which ultimately reduce the prevalence of CVDs.

Key Words: Cardiac markers; Hypertension; Pathogenesis; Prevalence; Cardiovascular diseases

Core Tip: The risk of cardiovascular disease (CVD) is increasing, and hypertension continues to be a significant global public health concern. Effective blood pressure control lowers the risk of stroke, heart attack, and heart failure. This review article explained the role of major cardiac markers (creatinine kinase-MB, cardiac troponins, lipoprotein a, osteopontin, cardiac extracellular matrix, C-reactive protein, cardiac matrix metalloproteinases, cardiac natriuretic peptides, myoglobin, renin, and dynorphin) in the pathogenesis of hypertension. The early identification of these cardiac markers and a therapeutic approach will help manage these cardiac markers in hypertensive subjects to reduce the prevalence of CVDs.

INTRODUCTION

The prevalence of cardiovascular disease (CVD) is rising on a global scale. One of the most significant risk factors for CVD is hypertension, which is frequently linked to metabolic syndrome, obesity, and both. A growing amount of focus is being paid to the search for the essential processes that connect high blood pressure (BP), glucose and lipid dysmetabolism, increased risk of CVD, and mortality[1].

Cardiac markers also called biomarkers are used to evaluate heart function and are measured, which are useful for the early prediction as well as diagnosis of disease. Early markers are also identified as enzymes and sometimes termed cardiac enzymes, but not all of the markers currently used are enzymes as in formal usage, and troponin (Tn) would not be listed as a cardiac enzyme[2,3].

In this regard, a study reported higher levels of cardiac markers, inflammation, as well as vasoconstrictors in runners with exercise-induced high BP. The scientists also noted that parameters linked to elevated BP in middle-aged marathon runners were related to increases in cardiac Tn I (cTnI), N-terminal pro-B-type natriuretic peptide (NT-proBNP), endothelin-1, and high-sensitivity C-reactive protein (hs-CRP) caused by the marathon. These associations were found without consideration of past running experience, completion rates, or peak oxygen intake[4].

Many cardiac biomarker levels become aberrant a long time before the manifestation of evident CVD, and mounting data show that cardiac biomarkers may play a special role in the prognostic evaluation of patients with hypertension. The authors provided a summary of cardiac biomarkers that could be utilized to predict the development of CVD in people with hypertension[5]. Similarly, Pasupathi *et al*[6] reported numerous biochemical markers in clinical cardiology. Also, Parsanathan *et al*[7] explained the evidence for the presence of traditional cardiac biomarkers. Interestingly, Vassiliadis *et al*[8] described novel cardiac-specific biomarkers and the CV continuum including creatinine kinase-MB (CK-MB), myoglobin, Lp (a) [lp (a)], brain NP (BNP), cTnI and cTn T (cTnT), osteopontin (OPN), CRP, cardiac extracellular matrix (ECM), cardiac matrix metalloproteinases (MMPs), and so on. However, this review article only reported CK-MB, cTn, Lp (a), OPN, cardiac ECM, CRP, MMPs, cardiac NPs, myoglobin, renin, and dynorphin role in the pathogenesis of hypertension as explained in Figure 1. This article explained the recent major advances as well as discoveries, significant gaps, and current debates and most importantly outlined ideas for future research.

To review the literature, various databases including Google Scholar, PubMed, and Science Direct were used. The search was completed on May 20, 2022. Cardiac markers, hypertension, and pathogenesis were just a few of the terms utilized to search the literature. The relevant articles' references were examined, and comparable articles were found. Clinical investigations could only be conducted in English. Despite favoring more recent studies, we did not set a time limit.

ROLE OF MAJOR CARDIAC MARKERS IN HYPERTENSION

There are many cardiac markers, but this article only highlighted pathophysiological aspects of the major cardiac markers such as CK-MB, cTn, Lp (a), OPN, cardiac ECM, CRP, MMPs, cardiac NPs, myoglobin, renin, and dynorphin in the pathogenesis of hypertension as explained in Tables 1-3.

CK AND CK-MB

Pressure responses are enhanced and BP is increased by high CK activity, particularly in resistance arteries[9,10]. In this context, Brewster *et al*[11] reported that after adjusting for age, sex, body mass
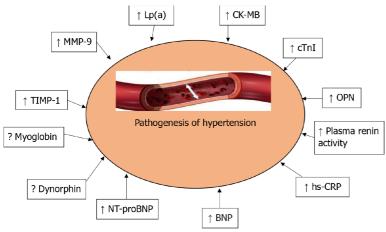
Table 1 Role of creatine kinase, creatine kinase-MB, cardiac troponin I, and lipoprotein (a) in the pathogenesis of arterial hypertension

Ref.	Cardiac markers	The main finding of cardiac markers in arterial hypertension
Brewster *et al* [11], 2006	Creatine kinase	Creatine kinase was independently associated with blood pressure, with an increase in systolic and diastolic pressure, respectively
Emokpae *et al* [12], 2017	Creatinine kinase-MB	The mean creatinine kinase-MB activity of the female hypertensive subjects was significantly higher than the males
McEvoy *et al* [13], 2015	High-sensitive cardiac troponin T	In an ambulatory population with no history of cardiovascular disease, high-sensitive cardiac troponin T was associated with incident hypertension and risk of left ventricular hypertrophy
Emokpae *et al* [12], 2015	Cardiac troponin I	The mean cardiac troponin I of the female hypertensive subjects was significantly higher than the males
Kim *et al*[14], 2022	Cardiac troponin I	Reported the elevated cardiac troponin I in the crisis of hypertensive patients which could provide useful prognostic information and permit the early identification of patients with an increased risk of death
Stefanie *et al* [15], 2015	High-sensitivity cardiac troponin I	The study concluded that an independent relation was found between high-sensitivity cardiac troponin I with systolic blood pressure as well as left ventricular hypertrophy
Sato *et al*[16], 2011	High-sensitivity cardiac troponin T	The high-sensitive cardiac troponin T was 78% of patients presenting with treated essential hypertension and independently correlated with age, renal function, and electrocardiogram voltage of hypertrophy
Afonso *et al* [18], 2011	Cardiac troponin I	Observed a disturbingly high incidence of mortality in individuals presenting with a hypertensive emergency, although neither the presence nor the extent of cardiac troponin I release was associated with greater odds of death
Acosta *et al* [19], 2020	Troponin	About one-third of patients with the hypertensive crisis have detectable troponin. Still, among these patients, less than half have troponin levels consistent with myocardial injury, and the majority of these patients have minimal changes in serial troponin
Tehrani *et al* [17], 2019	High-sensitive cardiac troponin T	An increase in high-sensitive cardiac troponin T over time is associated with a higher risk of cardiovascular disease even when the blood pressure is stable or decreases over time
Liu *et al*[22], 2021	Lipoprotein (a)	Elevated lipoprotein (a) was associated with an increased risk of A cerebrovascular events in stable coronary artery disease patients with hypertension. Moreover, the coexistence of high lipoprotein (a) concentrations and hypertension greatly worsened the clinical prognosis in patients with coronary artery disease, which may suggest a prognostic correlation between lipoprotein (a) and hypertension
Gazzaruso *et al*[23], 1996	Lipoprotein (a) levels and apo (a) isoforms	High lipoprotein (a) levels and apolp (a) isoforms of low molecular weight are strongly associated with a family history of coronary heart disease in hypertensives. The quantification of lipoprotein (a) levels and the character-ization of apo (a) phenotypes may be used for the assessment of familial predisposition to coronary heart disease in hypertensives
Catalano *et al* [24], 1998	Lipoprotein (a)	Higher plasma concentrations of lipoprotein (a), albeit within the normal range, could be an independent risk factor for atherosclerosis and could contribute to increasing the incidence of cardiovascular disease in people with essential arterial hypertension.
Ghorbani *et al* [25], 2013	Lipoprotein (a)	There was a significant correlation between serum lipoprotein (a) and age or duration of high blood pressure
Antonicelli *et al*[26], 2001	Lipoprotein (a)	The study found a significant correlation was found between lipoprotein (a) levels and the night-time systolic and diastolic pressures as well as with the mean night-time fall in systolic and diastolic blood pressures
Drgan *et al* [27], 2011	Lipoprotein (a)	Lipoprotein (a) was significantly higher in the hypertension group than in the hypertension group and then in the control group
Sechi *et al*[28], 1997	Lipoprotein (a)	Reported that lipoprotein (a) levels, as well as apolipoprotein (a) phenotype, have also been shown to be related to target organ damage in patients with essential hypertension, with a higher frequency of the low molecular weight apo (a) phenotype in patients with increasing severity of target organ damage
Ward *et al* [29], 2021	Lipoprotein (a)	Authors suggested that in approximately 30% of the patients in this risk, lipoprotein (a) level is elevated in the hypertensive cohort and measurement of lipoprotein (a) could be useful in risk stratification
Woo *et al*[31], 1991	Lipoprotein (a)	The study showed a history of hypertension, a high serum lipoprotein(a) concentration, and a low apolp (a)-I concentration to be independent risk factors for all strokes

index (BMI), and ethnicity, the independent relationship between CK and BP showed an increase in systolic and diastolic BP of 8.0 mmHg (95% confidence interval [CI]: 3.3 to 12.7) and 4.7 (95%CI: 1.9 to 7.5) and 4.7 mmHg (95%CI: 1.9 to 7.5), respectively. In another study, Emokpae *et al*[12] observed that the mean CK-MB activity was significantly elevated in hypertensive females compared with males. By contrast, the mean CK-MB activity was significantly lower for normotensive female subjects than for the male counterparts. In hypertensive individuals, serum CK-MB activity was higher in females than in males. Additionally, cardiac indicators should be routinely performed in the assessment of hypertension subjects, and sex-specific considerations may be recognized in the therapy of these patients[12].

Table 2 Role of osteopontin, extracellular matrix, and C-reactive protein in the pathogenesis of arterial hypertension

Ref.	Cardiac markers	The main finding of cardiac markers in arterial hypertension
Caesar *et al* [32], 2016	Osteopontin expression	The study found that hypertension-induced elevated in osteopontin expression was inhibited in transgenic smooth muscle cell-specific catalase overexpressing (Tg$^{SMC-Cat}$) mice
Yang *et al* [34], 2020	Osteopontin	Circulating osteopontin was an independent risk factor for both left ventricular hypertrophy and left ventricular diastolic dysfunction in essential hypertensive patients
Caesar *et al* [35],	Osteopontin	Osteopontin is upregulated with mechanical strain in smooth muscle cells and the aorta with hypertension through hydrogen peroxide
Bellan *et al* [36], 2021	Osteopontin	Osteopontin was significantly associated with pulmonary arterial hypertension among patients with connective tissue diseases
Cai *et al*[39], 2021	Extracellular ma-tri	Extracellular matrix remodeling in the component profiles, mechanical properties, degradation processes, and degraded fragment production leads to subsequent vascular wall structural and functional remodeling and results in hypertension
Smith *et al* [43], 2005	C-reactive protein	C-reactive protein concentrations are linked with hypertension, and pulse pressure, but adjustment for life course confounding and the Mendelian randomization approach suggests that higher C-reactive protein levels do not lead to higher blood pressure
Hage *et al* [44], 2013	C-reactive protein	Explained the role of C-reactive protein in hypertensive individuals which is linked with vascular stiffness, atherosclerosis and the development of end-organ damage and cardiovascular events
Sesso *et al* [45], 2003	C-reactive protein	C-reactive protein levels are connected with future development of hypertension, which suggests that hypertension is in part an inflammatory disorder
Lakoski *et al* [46], 2005	C-reactive protein	The study confirms the existence of an independent association between hypertension and inflammation in both men and women. Ethnic group differences were evident, with the strongest association observed in Chinese participants and no difference in C-reactive protein levels by hypertension status in Hispanics
Pan *et al*[47], 2019	High-sensitivity C-reactive protein	High-sensitivity C-reactive protein is prevalent in Yi people and does not support high-sensitivity C-reactive protein as a risk factor for prehypertension or hypertension
Shao-Yuan *et al*[49], 2013	C-reactive protein	The concentration of C-reactive protein was associated with systolic pressure and pulse pressure, but not with diastolic blood pressure
Van *et al* [50], 2022	C-reactive protein	The association between C-reactive protein and hypertension among Ghanaian migrants and urban-Ghanaian women, however, was largely explained by conventional risk factors. Thus, prevention of conventional risk factors, in particular obesity, may help to reduce the potentially low-grade inflammatory mechanism underlying hypertension

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Figure 1 Overview of major cardiac markers' role in the pathogenesis of hypertension. Source: Designed by the authors with the help of articles, signs showed further information, *e.g.*, ↓ - decreased levels, ↑ - increased levels. BNP: Brain natriuretic peptide; CK-MB: Creatinine kinase-MB; CRP: C-reactive protein; cTnI: Cardiac troponin I; lp (a): Lipoprotein A; OPN: Osteopontin; MMPs: Matrix metalloproteinases; NPs: Natriuretic peptides; NT-proBNP: N-terminal-pro hormone BNP; TIMPs: Tissue inhibitors of metalloproteinases.

cTn

The female participants with hypertension had a mean cTnI that was substantially greater than that of the males. Between male and female normotensive patients, there was no difference in levels of cTnI [12]. No history of CVD in an ambulatory population and high-sensitivity cTnT (hs-cTnT) is linked to incident hypertension as well as the risk of left ventricular hypertrophy (LVH). According to the

Table 3 Role of matrix metalloproteinases, tissue inhibitors of metalloproteinases, N-terminal pro-B-type natriuretic peptide, plasma renin activity levels, and dynorphin in the pathogenesis of arterial hypertension

Ref.	Cardiac markers	The main finding of cardiac markers in arterial hypertension
Prado *et al*[52], 2021	Matrix metalloproteinase activity	Imbalanced vascular matrix metalloproteinase activity promotes vascular dysfunction and a variety of structural alterations, resulting in vascular remodeling in hypertension
Flamant *et al*[53], 2007	Matrix metalloproteinase-9 activity	The onset of angiotensin II-induced hypertension is accompanied by increased matrix metallo-proteinase-9 activity in conductance vessels; absence of matrix metalloproteinase-9 activity results in vessel stiffness and increased pulse pressure; and matrix metalloproteinase-9 activation is associated with a beneficial role early on in hypertension by preserving vessel compliance and alleviating blood pressure increase
Hopps *et al*[54], 2017	Matrix metalloproteinases and tissue inhibitors of metallopro-teinases	The authors believe that in clinical practice a strategic antihypertensive therapy directed to the matrix metalloproteinase profile may be useful to decrease the risk of cardiovascular complic-ations
Valente *et al*[55], 2020	Matrix metalloproteinase-9 concentrations	Matrix metalloproteinase-9 concentrations are significantly higher in the hypertensive crisis groups (urgency and emergency) compared to the control groups. Therefore, matrix metallopro-teinase-9 may be a biomarker or mediator of pathophysiologic pathways in cases of acute elevations of blood pressure
Kuliczkowski *et al* [56], 2019	Tissue inhibitors of metallopro-teinases-4, matrix metallopro-teinase-2	Data showed that patients with coronary artery disease presented higher tissue inhibitors of metalloproteinase-4 and lower matrix metalloproteinase-2 concentrations regardless of hypertension and diabetes mellitus.
Tayebjee *et al*[57], 2004	Matrix metalloproteinase-9, tissue inhibitor of metalloproteinase-1	Increased circulating matrix metalloproteinase-9, tissue inhibitor of metalloproteinase-1 at baseline in patients with hypertension could reflect an increased deposition and retention of type I collagen at the expense of other components of extracellular matrix within the cardiac and vascular extracellular matrix
Robert *et al*[58], 1997	Matrix metalloproteinases	Observations suggest that depression of the degradative pathway is partly responsible for age-associated fibrosis. Thus, matrix metalloproteinase has differing involvements in the cardiac remodeling associated with hypertension or aging
Marchesi *et al*[61], 2012	Matrix metalloproteinase-2, matrix metalloproteinase-9, tissue inhibitor of metalloproteinase-1	Suggested that matrix metalloproteinase-2, matrix metalloproteinas-9 as well as tissue inhibitor of metalloproteinases-1 could have a role as biomarkers of cardiovascular remodeling in hypertension patients
Nakatsu *et al*[64], 2007	Plasma B-type natriuretic peptide	Hypertensive patients with abnormal diurnal blood pressure variation patterns (non-dippers, extreme dippers, and risers) showed higher plasma B-type natriuretic peptide levels than those with normal circadian blood pressure variation (dippers)
Seven *et al*[65], 2015	N-terminal pro-B-type natriuretic peptide	Elevated serum concentrations of N-terminal pro-B-type natriuretic peptide are associated with prevalent hypertension whereas lower concentrations associate with incident hypertension
Freitag *et al*[66], 2003	Plasma brain natriuretic peptide	Higher plasma brain natriuretic peptide levels were associated with an increased risk of blood pressure progression in men but not women
Brunner *et al*[69], 1972	High plasma renin activity	Essential hypertension would appear to show that individuals with low plasma renin activity had a significantly lower incidence of myocardial infarction and stroke over about 10 years of observation compared to individuals with normal or high plasma renin activity
Sever *et al*[70], 2012	Plasma renin activity levels	Elevated plasma renin activity levels in a hypertensive population with no pre-existing cardiovascular disease do not indicate the future occurrence of cardiovascular events
Haber *et al*[71], 1979	Renin	Renin is crucial for regulating blood pressure in the salt- or volume-depleted condition and is in charge of the early stages of renovascular hypertension
Laragh *et al*[74], 2011	Plasma renin activity	Plasma renin activity testing can be used to guide the commencement, addition, or subtraction of anti-sodium-volume dependent or anti-renin-angiotensin antihypertensive drug types in hypertensive patients
Fontana *et al*[78], 1993	Dynorphin	Dynorphin modulates sympathetic activity *via* stimulation of atrial natriuretic factor which can reduce BP in hypertensive subjects
McConnaughey *et al*[79], 1992	Dynorphin	Findings imply that alterations in the opioid system's hippocampus receptors may be important for the main blood pressure-control mechanism
Wang *et al*[80], 1994	Dynorphin-A (1-8)	Dynorphin-A (1-8) injected into the hippocampal formation causes a significant drop in blood pressure in conscious hypertensive and normotensive rats, but not heart rate

authors, to determine if hs-cTNT can identify people who could benefit from ambulatory BP monitoring or hypertension preventive lifestyle changes[13].

Elevated cTnI during a hypertensive patient crisis may offer helpful prognostic data and allow for the early identification of patients at higher risk of dying. In the groups with high, detectable, and undetectable cTnI, the 3-year all-cause death rates were 41.6%, 36.5%, and 12.8%, respectively. Additionally, a higher risk of death from all causes was substantially linked to cTnI levels that were normal but detectable. Patients with hypertensive crises and increased and detectable cTnI levels need critical treatment and follow-up methods[14]. Equally important, Stefanie *et al*[15] concluded that an

independent relationship was found between hs-cTNT with systolic BP as well as LVH. Sato *et al*[16] explained that hs-cTNT was 78% of patients presenting with treated essential hypertension and independently correlated with age, renal function as well as electrocardiogram voltage of hypertrophy. Further, Tehrani *et al*[17] reported an elevated range of hs-cTNT over time, which is linked to a higher risk of CVD even when the BP is stable or decreases over time. Moreover, Afonso *et al*[18] observed a disturbingly elevated incidence of mortality in individuals representing a hypertensive emergency, although neither the presence nor extent of cTnI release was linked to greater odds of death.

Tn is detectable in about one-third of patients with hypertensive crises. Nevertheless, less than half of these patients have Tn levels that are compatible with myocardial damage, and the majority of them show little change in sequential Tn. Aspirin use, previous cardiac hippocampal formation, and low BMI are all independently linked to myocardial damage in these patients. Higher initial and serial Tn are strongly correlated with lower BMI. The significant inverse relationship between BMI and myocardial damage is more pronounced in-patient populations who are older and female. These findings contribute to the understanding of the pathophysiology, risk factors, and clinical significance of baseline and ongoing Tn levels in patients with hypertensive crisis[19].

LIPOPROTEIN A

Various epidemiological, as well as genetic studies, have identified a higher concentration of lipoprotein (a) [lp (a)] as a causal and independent risk factor for CVD. The lp (a)-induced elevated risk of CVD could be mediated by both its prothrombotic and proatherogenic mechanisms[20]. In the same way, Reaven *et al*[21] showed observations that elevated the possibility that abnormalities of lipoprotein, as well as carbohydrate metabolism, could play a role in both the clinical as well as etiology course of hypertension.

Additionally, the risk of CV events was only significantly higher in the high Lp (a) as well as hypertension group compared with the reference group with low Lp (a) concentration and normotensive (hazard ratio: 1.80, 95%CI: 1.11–2.91). The higher Lp (a) was linked to an increased risk of CV events in stable coronary artery disease patients with hypertension. Additionally, the coexistence of high Lp (a) concentrations and hypertension greatly worsened the clinical prognosis in patients with coronary artery disease, which may recommend a prognostic correlation between Lp (a) and hypertension[22].

Lp (a) plasma concentrations, as well as apolipoprotein (apolp) (a) phenotype, did not differ between hypertensive and control groups. Higher Lp (a) plasma concentrations and apolp (a) isoforms of low molecular weight were strongly linked to a family history of coronary heart disease in hypertensives. The quantification of Lp (a) concentration and characterization of apoLp (a) phenotypes could be used for the assessment of familial predisposition to coronary heart disease in hypertensives[23].

The two main risk factors including hypertension and dyslipidemia for vascular diseases on an atherosclerotic basis were linked. However, even though they were within the normal range, higher Lp (a) plasma concentrations may be a separate risk factor for atherosclerosis and can increase the prevalence of CVD in persons with essential arterial hypertension[24].

Ghorbani *et al*[25] explained the significant correlation between serum Lp (a) and age or duration of hypertension (known duration of hypertension period). Also, the possibility that Lp (a) may play a role as a cofactor in essential hypertension has been raised, although the exact mechanism is still unclear[25].

The nighttime systolic and diastolic BP, as well as the mean nighttime decrease in systolic and diastolic BP, were significantly correlated with lp (a) levels. When peroxidative stress data were taken into account, these associations were further confirmed (r = 0.37 and r = 0.40, *P* = 0.01 for the nighttime decline in systolic and diastolic BP, respectively; r = 0.34 and r = 0.38, *P* = 0.01 for the nighttime increase in systolic and diastolic BP). This relationship did not affect the apolLp (a) isoform size. The authors explained that lp (a), as well as peroxidative stress, could be involved as cofactors in essential hypertension, with a mechanism that remains to be elucidated[26]. Whereas, Drgan *et al*[27] showed that lp (a) was significantly higher in hypertensive patients with atherogenic dyslipidemia group than in hypertensive patients without atherogenic dyslipidemia group compared to the control group. A significant correlation was found between Lp (a) and intima-media thickness between Lp (a) and fibrinogen, and between Lp (a) and brachial flow-mediated vasodilatation. Total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), apoLp A or B, or apoA-I/apoB levels did not correlate with Lp (a) levels[27].

Target organ damage has also been linked to Lp (a) levels and apoLp (a) phenotype in patients with essential hypertension, with a higher prevalence of the low molecular weight apoLp (a) phenotype in individuals with progressive target organ damage. These connections did not seem to be related to BP [28]. Moreover, Ward *et al*[29] suggested that in approximately 30% of the patients in this risk, Lp (a) level was elevated in the hypertensive cohort and measurement of Lp (a) could be useful in risk strati-fication.

Additionally, Chan *et al*[30] concluded that elevated Lp (a), hypertension and renal insufficiency are independent risk factors beyond elevated pretreatment LDL-C, which predict coronary artery disease in

patients with familial hypercholesterolemia. Despite the cross-sectional design, the authors proposed the need for identifying and managing these abnormalities to reduce excess coronary artery disease risk in familial hypercholesterolemia patients. However, this proposal remains to be formally tested in a prospective study[30]. Woo *et al*[31] revealed that the independent risk factors for all strokes were a history of hypertension, high serum Lp (a) concentration, and low apoLp (a)-I concentration.

OPN

Hypertension is a known risk factor for the processes of atherosclerosis and has a direct impact on vascular hypertrophy. The most important protein mediator of inflammation is OPN, which also has a role in remodeling of large arteries. In the same way, according to a study, transgenic mice that specifically overexpress catalase in smooth muscle cells (Tg$^{SMC-Cat}$) prevent the enhanced OPN expression that hypertension causes. Additionally indicating that hydrogen peroxide is crucial in mediating the rise in OPN expression brought on by hypertension. These findings indicate that OPN may play a crucial role in the pathogenesis of hypertension[32].

In the same context, Matsui *et al*[33] reported that consequently, wild-type mice underwent angiotensin II (Ang II) therapy, which led to markedly increased BP and heart hypertrophy and fibrosis. The development of cardiac fibrosis and BP increase caused by Ang II could be reduced with eplerenone (Ep) medication and OPN deficiency, whereas the development of cardiac hypertrophy could be prevented with Ep alone. Most convincingly, in OPN-deficient animals treated with Ang II, the reduction of cardiac fibrosis resulted in impaired cardiac systolic function and consequent LV dilatation. These findings indicate that OPN is essential for the fibrosis and remodeling of the heart caused by Ang II. Additionally, the reduction of OPN expression may have a role in the action of Ep on the prevention of cardiac fibrosis but not ventricular hypertrophy[33]. Yang *et al*[34] concluded that circulating OPN is an independent risk factor for both LV hypertrophy and LV diastolic dysfunction in essential hypertensive patients. However, OPN is not associated with LV dimension and systolic function[34].

Also, Caesar *et al*[32] showed that through hydrogen peroxide, OPN is upregulated with mechanical stress in smooth muscle cells and the aorta with hypertension. Authors have demonstrated that it is crucial in modulating aortic remodeling and inflammation. Overall, these findings contribute to the understanding of vascular inflammation and have significant implications for the development of future treatments and prevention measures for the side effects of hypertension, such as atherosclerosis[35]. Moreover, OPN is significantly associated with pulmonary arterial hypertension among patients with connective tissue diseases, suggesting that it may have a role as a non-invasive disease biomarker of pulmonary arterial hypertension[36].

CARDIAC ECM

Through modulating collagen synthesis, degradation, and cross-linking, T lymphocytes may play a crucial regulatory function in the composition of the cardiac ECM[37]. Briones *et al*[38] stated that vascular stiffness and fibrosis can be treated with currently available antihypertensive medications. Insights into cutting-edge treatments to lessen arterial stiffness and new applications for currently available antihypertensive medications will come from a deeper knowledge of the molecular mechanisms behind changes in the ECM in hypertension[38]. In the same way, Cai *et al*[39] explained that hypertension is the outcome of subsequent structural and functional remodeling of the arterial wall caused by the ECM, which alters the component profiles, mechanical properties, degradation processes, and creation of degraded fragments. According to scientists, more studies involving the application of matridomic and degradomic techniques may offer proof for the identification of various ECM components. Improved comprehension of vascular matrix biology and the complex mechanisms underlying hypertension may offer fresh perspectives on the formation of antihypertensive treatments [39].

CRP

In complex mechanisms that result in endothelial dysfunction, CRP plays a role in elevated peripheral vascular resistance and stiffness of the major arteries in hypertension[40]. Various studies have reported that higher concentrations of hs-CRP in healthy subjects are associated with an elevated risk of upcoming stroke, peripheral arterial disease, heart attack, sudden cardiac death, and cardiac events in coronary artery disease patients with obesity, colon cancer, and complications of diabetes[41]. The levels of hs-CRP could correspond to the extent of risk of recurrent acute coronary syndrome, heart failure decompensation/development, the size of myocardial necrosis area, ventricular tachycardia, the risk of new-onset atrial fibrillation, and death in patients with association of medical illustrators[42].

Additionally, Smith *et al*[43] stated that CRP concentrations were linked to hypertension and pulse pressure, but adjustment for life course confounding and the Mendelian randomization approach suggested that higher CRP levels did not lead to higher BP[43].

In hypertensive individuals, CRP has a role in vascular stiffness, atherosclerosis, the onset of end-organ damage, and CV events. CRP has also higher concerns as a modulator of cardiac and vascular remodeling in response to pressure overload and damage, respectively[44]. Also, Sesso *et al*[45] concluded that CRP levels are associated with the development of hypertension in the future, indicating that inflammation may play a role in the development of hypertension. Lakoski *et al*[46] reported the presence of a separate link between inflammation and hypertension in both sexes. The largest correlation was found in Chinese individuals, whereas there was no variation in CRP levels by hypertension status in Hispanics. Ethnic group differences were clear[46]. Likewise, Pan *et al*[47] suggested that Yi people frequently have elevated hs-CRP, which did not indicate that it is a risk factor for prehypertension or hypertension.

Lack of vitamin D increases levels of the inflammatory markers such as hs-CRP and LDL, and high levels of oxidized LDL are all associated with pulse pressure amplification in people with high BP. In middle-aged hypertensive and high normal BP patients, vitamin D levels, high-sensitivity CRP, and LDL provide useful information regarding arterial stiffness and early arterial old age; however, only hsCRP is a sensitive predictor of early arterial old age and pulse wave velocity[48].

Shao *et al*[49] showed that by increasing CRP, the incidence rates of hypertension were 9.3, 19.0, and 33.0 per 1000 person-years. Baseline CRP remained strongly predictive of incident hypertension in the multivariate model that was controlled for age, sex, and prehypertension. The concentration of CRP was connected with systolic BP and pulse pressure, but not with diastolic BP. In conclusion, the authors explained the link between inflammation with future systolic BP in the Taiwanese population[49].

In the same context, van Apeldoorn *et al*[50] showed that the relationship between CRP levels and hypertension was varied by sex and geographical location. In age-adjusted models, there was an association between high CRP levels and hypertension in urban-Ghanaian women, European-Ghanaian men, and women. Nevertheless, these relationships were attenuated after adjustment for conventional risk factors, especially BMI. No association was found between rural Ghanaians and urban-Ghanaian men[50].

MMPs

MMPs, which are involved in a variety of physiological and pathological processes, are the most significant extracellular enzymes. Specific MMPs alter activity and concentration, as well as the imbalance with their inhibitors, such as tissue inhibitors of metalloproteinases (TIMPs), have all been attributed to the pathogenic cascade induced by arterial hypertension. The ECM contains a variety of protein substrates that MMPs can break down. By doing so, they can affect endothelial cell function, vascular smooth muscle cell migration, proliferation, contraction, and determination of alterations in cardiomyocytes. Chronically high BP values can activate all of these mechanisms. Studies on animals and people have demonstrated that, in addition to age and BP readings, MMPs play a critical role in the pathogenesis of hypertension-mediated vascular, cardiac, and renal damage. As a result, there is growing evidence supporting the use of MMPs as indicators of organ damage caused by hypertension and possible targets for pharmacological treatments to stop future CV and renal problems in the hypertensive population[51].

Prado *et al*[52] stated that unbalanced vascular MMP activity boosts vascular dysfunction and several structural changes, leading to vascular remodeling in hypertensive individuals. Recently, it has become clearer how protective MMP inhibitors, antioxidants, and medications increase vascular nitric oxide activity, and new treatments are emerging that address these crucial mechanisms, which may provide significant benefits in preventing the vascular remodeling of hypertensive patients.

In the same context, Flamant *et al*[53] explained the cause of the beginning of Ang II-induced hypertension and increased MMP-9 activity in conductance vessels. Similar to how MMP-9 activation results in vascular stiffness and increased pulse pressure, so does its absence. Similar to MMP-8 activation, MMP-9 activation is associated with an early, beneficial effect on hypertension by maintaining vascular compliance and reducing a BP increase[53].

Human hypertension impairs the production and activity of a few MMPs and TIMPs. In response to hemodynamic alterations that may cause cardiac hypertrophy and fibrosis, leading to ventricular remodeling, the altered MMP/TIMP balance plays a critical role in the rearrangement of the vascular wall. Numerous studies have investigated the effects of some antihypertensive molecules on the MMP/TIMP profile and found positive results. These molecules include angiotensin converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, and aldosterone antagonists. A selective antihypertensive therapy focused on the MMP profile, according to the authors, may also be helpful in clinical settings to lower the risk of CV problems[54].

When compared to the control groups, the hypertensive crisis groups (urgency and emergency) have considerably greater MMP-9 concentrations. Therefore, MMP-9 may be a biomarker or modulator of

pathophysiologic pathways in situations involving abrupt increases in BP[55]. By contrast, Kuliczkowski *et al*[56] showed that patients with coronary artery disease present with higher TIMP-4 and lower MMP-2 concentrations regardless of arterial hypertension and diabetes mellitus (DM). Arterial hypertension did not affect MMP-2, MMP-9, and TIMP-4 levels in serum. Higher MMP-2 concentration was independently linked to the onset of diabetes; however, the coexistence of DM and coronary artery disease was linked to a balance in MMP-2 level. None of the groups under study noted a significant change in MMP-9 concentration[56].

Moreover, Tayebjee *et al*[57] showed that circulating pretreatment MMP-9 and TIMP-1 levels in hypertensive patients were considerably higher than levels in normotensive controls. Following therapy, plasma MMP-9 levels were decreased but TIMP-1 levels were increased. MMP-9 levels did not correlate with cardiovascular accident (CVA) risk but did with HDL-C and coronary heart disease (CHD) risk. TIMP-1 scores did not significantly correlate with CVA or CHD scores[57].

The vascular remodeling that occurs in the early stages of hypertension is significantly influenced by MMPs. Still, as people age, MMP-2 and proMMP-1 activity decrease by 40% and 45%, respectively, with a corresponding downregulation of MMP-2 mRNA. These findings indicate that age-related fibrosis is partially caused by depression of the degradative pathway. As a result, MMP plays a variety of roles in the heart remodeling carried on by hypertension or age[58].

MMPs are pharmacological targets in hypertension. It is still unknown if the circulating MMP concentration in hypertension accurately reflects tissue levels. If this is the case, circulating MMPs could be used to identify people who are more likely to experience CV problems as a result of their hypertension. Early therapeutic intervention, such as the use of MMP inhibitors, may be beneficial for these patients. To explain the predictive relevance of MMPs and tissue inhibitors of metalloproteinases in hypertension, well-designed and controlled clinical studies are essential[59].

The myocardium's MMPs are a significant biological system responsible for maintaining the ECM's complex and dynamic milieu. A deeper understanding of how this system is dysregulated in hypertensive heart disease will likely lead to fresh perspectives on treatment options for heart failure [60].

In patients with hypertension, the TIMP-1, MMP-2, and MMP-9 may serve as indicators of CV remodeling. If these findings are supported by future clinical research, they may offer a novel method for stratifying CV risk in hypertensive individuals[61].

CARDIAC NPs

The three known NPs are atrial NP (ANP), BNP, and C-type NP, all of which play a role in the control of CV homeostasis through their diuretic, natriuretic, and vasodilatory activities. The effects of ANP on controlling BP and cardiac function have drawn a lot of interest. No pharmacological strategy directly targeted at modulating ANP levels has ever advanced to the point of being incorporated into clinical practice, despite numerous clinical and experimental studies evaluating the potential role of ANP in therapeutic application for the treatment of hypertension and heart failure. A potential CV risk factor for stroke, metabolic syndrome, hypertension, and obesity has been identified as an ANP. In the meantime, BNP has become an important indicator of LV dysfunction and a helpful indicator of future outcomes in heart failure patients[62].

In the porcine brain, BNP was first investigated and then isolated from porcine, rat as well as human hearts. The increased severity of hypertension, importantly when LVH is present, plasma BNP levels are progressively increased in humans. This is due to increased production and constitutive release of BNP from ventricular tissue, which results in increases in ventricular mass. Furthermore, plasma levels of BNP could serve as indicators of hypertensive LVH. In hypertensive patients, acute injection of BNP significantly increases natriuresis while suppressing plasma aldosterone. However, additional research is required to fully understand the pathophysiological role of BNP in essential hypertension[63].

Nakatsu *et al*[64] concluded that compared to hypertensive patients with typical circadian BP fluctuation, those with irregular diurnal BP variation patterns (non-dippers, extreme dippers, and risers) displayed greater plasma levels of BNP (dippers). Clinically useful for identifying hypertensive individuals who have aberrant circadian BP variability, which raises the risk of CV events, is the plasma BNP level[64]. Furthermore, another study stated that elevated serum concentrations of NT-proBNP are associated with prevalent hypertension whereas lower concentrations are associated with incident hypertension. In addition, the authors proposed that decreased vasodilation and natriuresis brought on by a lower level of circulating BNP may contribute to the etiology of early-stage hypertension[65].

Freitag *et al*[66] reported that increased plasma BNP level is related to an increased risk of BP progression in males but not in women in multivariate models controlling for known risk variables. Neither men's nor women's BNP categories showed any apparent trends toward an increase in the prevalence of hypertension. Furthermore, the authors pointed out that greater plasma levels of BNP were linked to a higher risk of BP advancement in males but not females. To confirm these results and clarify the causes of these sex-related variances, further research is necessary[66].

Given their impact not only on BP management but also on glucose and lipid metabolism, cardiac NPs such as ANP and BNP may be essential in maintaining CV homeostasis and cardiac health. CVD and salt balance effects, along with all of the metabolic functions of cardiac NP, may play a substantial role in lowering total CV risk. Therefore, one of the key targets to treat these various linked disorders, as well as to lower hypertension and metabolically related CV risk, may be the cardiac NP system. It has two receptors and a neutralizing enzyme[1].

RENIN

Renin is an important hormone that regulates several physiological processes, including BP. Even though renin was first discovered over a century ago, a better knowledge of the origin of renin-producing cells and the mechanisms responsible for renin synthesis and secretion has only recently been achieved. The main source of renin is juxtaglomerular cells (JGCs), which release renin from storage granules. Local renin-angiotensin systems are additionally found in several tissues in addition to the renin-angiotensin system in JGCs[67].

It has been widely studied how the sympathetic nervous system and renin-angiotensin-aldosterone system (RAAS) interact to cause CVD. Renin is the first RAAS limiting step, and there is ongoing discussion about how it might be used as a biomarker to enhance CV risk stratification. Elevated plasma renin activity has been linked to higher morbidity and mortality in individuals with CVD[68].

The earliest study by Brunner *et al*[69] in a small study of individuals with essential hypertension showed that over about 10 years of observation, individuals with low plasma renin activity had a significantly lower incidence of myocardial infarction and stroke compared to individuals with normal or high plasma renin activity[69]. Elevated plasma renin activity levels in a hypertensive population without pre-existing CVD do not predict the future occurrence of CV events, in contrast to what has been reported in patients with established CHD or heart failure[70].

Furthermore, Haber *et al*[71] reported that renin is crucial for regulating BP in a salt- or volume-depleted condition and controls the early stages of renovascular hypertension. If salt does or does not build up, renin's role in chronic renovascular hypertension will vary. Renin continues to play a substantial role during the chronic phase if sodium intake is controlled or if sodium excretion is unaffected (such as in two-kidney renovascular hypertension models)[71]. Although participation of the RAAS in the pathophysiology of essential hypertension is unclear, there is an increased number of data to support it, partly because it stimulates the production of reactive oxygen species, which harm target organs[72,73].

To improve BP control and prognosis while lowering medication type consumption and expense, plasma renin activity testing can be used to guide the commencement, addition, or subtraction of anti-sodium-volume-dependent or anti-renin-angiotensin antihypertensive drug types in hypertensive patient[74].

DYNORPHIN

The precursor protein prodynorphin gives rise to a group of opioid peptides known as dynorphins. Dynorphin A, dynorphin B, and/-neoendorphin are among the active peptides that are generated when prodynorphin is cleaved by proprotein convertase 2[75]. Dynorphin plays a role as an endogenous hypotensive peptide in healthy rats[76] and those that undergo subsequent bradycardia[77]. Notably, dynorphin modulates sympathetic activity *via* stimulation of AN factor[78], which can reduce BP in hypertensive subjects.

Another study reported that spontaneously hypertensive rats and Wistar-Kyoto (WKY) at ages 4, 8, 12, and 16 had their hippocampus membrane preparations' dynorphin receptor binding sites examined. Compared to WKY controls, spontaneously hypertensive rats displayed a substantial increase in hippocampus dynorphin receptor binding sites by the time they were 4-wk-old before hypertension became apparent. However, spontaneously hypertensive rats displayed significantly fewer hippocampal binding sites than Wistar-Kyoto rats at 8, 12, and 16 wk of age, when hypertension is detectable. At any age, there were no differences in the two strains of rats' receptor affinities for dopamine. These findings indicate that alterations in the opioid system's hippocampus receptors may be important for the main BP-control mechanism[79].

Furthermore, Wang *et al*[80] showed that dynorphin-A (1-8) injected into the hippocampal formation causes a significant drop in BP in conscious hypertensive and normotensive rats but not heart rate[80]. Another study showed that in hypotensive piglets, indomethacin (5 mg/kg intravenous) potentiated beta-endorphin-induced constriction and the constriction brought on by dynorphin while blocking methionine and leucine enkephalin, dynorphin, and pial arteriolar dilatation[81].

CONCLUSION

This review article concludes that major cardiac markers including CK-MB, cTn, Lp (a), OPN, cardiac ECM, CRP, cardiac MMPs, cardiac NP, renin, and dynorphin play a significant role in the pathogenesis of arterial hypertension. Additional studies are needed to find the association between myoglobin and other cardiac markers in hypertension. Moreover, therapeutic approaches are required to determine the early control of these cardiac markers, which ultimately reduce the prevalence of CVDs.

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FOOTNOTES

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