Inflammation Markers in Essential Hypertension

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Abstract: Essential hypertension is a common health disorder with uncertain etiology and unclear pathophysiology. There is evidence that various systems interact in uncertain ways and mechanisms to cause hypertension. It is also well known that inflammation is a key feature in the initiation, progression and clinical implication of several cardiovascular diseases. Recently, it has become evident that the immune system and inflammatory response are also essential in the pathogenesis of hypertension.

Many inflammation markers such as CRP, cytokines, and adhesion molecules have been found elevated in hypertensive patients supporting the role of inflammation in the pathogenesis of hypertension. Also, in normotensive individuals, these markers have been associated with the risk of developing hypertension, whereas in hypertensive patients they have been associated with target organ damage as well as with the risk for future cardiovascular events. Thus, understanding the role of inflammation in hypertension provides new insights for novel therapeutic approaches, targeting inflammation for the treatment of hypertension and its complications.

Keywords: Adhesion molecules, biomarkers, CRP, cytokines, hypertension, inflammation, target organ damage, treatment.

INTRODUCTION

Essential hypertension is a common health disorder with high prevalence reaching 30-45% of the general population among European countries and increasing with age, while its etiology and pathophysiology still remain undefined and unclear. In 90-95% of the patients hypertension can be classified as “primary/essential”, with heterogeneous, multifactorial and elusive etiology and only in 5-10% of them the cause is a known and identifiable factor (secondary hypertension) [1, 2]. Hypertension is an important risk factor for cardiovascular disease morbidity and mortality and an important public health challenge due to the enormous health and economic burden, despite the widely available anti-hypertensive treatments [3, 4].

Various systems interact in uncertain ways to cause hypertension and three components, -vascular dysfunction, renal impairment, and altered sympathetic outflow- have been found to play a pivotal role in the development and maintenance of elevated blood pressure [5]. Recently, increasing evidence suggests that the immune system and inflammatory response are also essential in the pathogenesis of hypertension [6].

Inflammatory process in hypertension is a complex response of the immune system that consists of interactions between inflammatory cells, such as macrophages and T lymphocytes, leading to increased expression of adhesion molecules, cytokines, matrix metalloproteinases and growth factors (Fig. 1) [7, 8]. These molecules guide the adaptive immune response and the migration of the immune cells to target tissues and promote the binding, rolling and infiltration of the immune cells into vascular wall and translocation to end organs. Inflammatory response involves not only the perivascular adipose tissue and vascular wall, leading to remodeling and impaired vascular function but also the heart (causing vasoconstriction and ischemia), the kidneys (causing renal vasoconstriction and renal injury) and the central nervous system, as animal and human studies have shown [9-13].

Studies have also suggested that hypertension exerts pro-inflammatory actions through increased expression of several inflammatory mediators including endothelin-1 and angiotensin. Apart from angiotensin II association with vasoconstriction and salt and fluid homeostasis, its role is equally important in the vascular inflammation and oxidative stress [14, 15]. Specifically, angiotensin II increases pro-inflammatory nuclear factor-kappa-B-dependent gene expression and stimulates the expression of various inflammatory molecules such as chemokines, cytokines and adhesion molecules and through activating nicotinamide-adenine dinucleotide phosphate (NADPH) oxidase, promotes the generation of reactive oxygen species [10,16]. Consequently, the detection and monitoring of inflammation markers that are involved in the pathogenesis of hypertension are of great scientific interest for the diagnosis and prognosis of cardiovascular disease [17, 18].
In this review, we will summarize the evidence of the pathophysiological connection between inflammation and essential hypertension focusing on traditional and novel inflammatory markers and the new insights for novel anti-inflammatory therapeutic approaches for the treatment of hypertension and its complications.

**CRP**

C-reactive protein (CRP) is a 115-kDa pentamer synthesized under the control of interleukin (IL)-6, in hepatocytes, although it can also be produced extrahepatically in kidney and adipose tissue, in the setting of innate, non-specific immune response to several pathophysiological conditions such as inflammation, infection, cell damage, apoptosis, and neoplasms [19].

Despite being an inflammatory marker, CRP may also play an important role in vascular inflammation as a promoter of pro-inflammatory and pro-atherogenic process. Additionally, it is the most stable inflammation marker with no circadian variations and therefore the most studied in cardiovascular disease. Specifically, CRP has various effects on the vascular endothelium including expression of adhesion molecules, chemokines and monocyte chemotactic protein-1 (MCP-1), plasminogen activator inhibitor-1 (PAI-1), matrix metalloproteinases and endothelin-1, whereas it decreases the production of nitric oxide (NO), prostacyclin and tissue plasminogen activator (tPA) [19, 20].

Several epidemiological studies have examined the relationship between CRP levels and cardiovascular risk in individuals without known cardiovascular disease and have shown CRP to be an independent cardiovascular risk factor [21].

Particularly, in a recent meta-analysis of 54 prospective studies including individuals without history of cardiovascular disease, CRP exhibited a strong log-linear relation with the risks of coronary artery disease (CAD), ischemic stroke and vascular and non-vascular mortality [22].

Several cross-sectional and prospective studies have shown, after adjustment for potential confounders, that CRP is increased in hypertensive patients, and its levels predict the onset of hypertension [23-30]. Batista et al. were the first to report higher CRP levels in hypertensive patients than in normotensive, independently of the influence of several CRP covariates such as age, body mass index (BMI), fasting glycaemia, sedentary behavior, alcohol consumption and family history of hypertension [23]. Furthermore, Sesso et al. in a cohort study regarding females from the Women's Health Study reported that after a median follow-up period of 7.8 years, about 26.1% of the enrolled women developed hypertension, and CRP was independently associated with an increased risk of developing hypertension, even in those women with very low initial systolic and diastolic blood pressure or without traditional cardiovascular risk factors [28]. More recently, Kong et al. demonstrated that CRP lev-

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**Fig. (1).** In normotensive conditions, when innate immunity is not activated, macrophages are not stimulated and will not produce tumour necrosis factor (TNF-α). Accordingly, antigen-presenting cells (APCs, dendritic cells [DCs]) have an anti-inflammatory or immune suppressant phenotype, and stimulate the commitment of naive T lymphocytes to the T regulatory cell (Treg) lineage. These T lymphocytes produce the anti-inflammatory interleukin (IL)-10 and transforming growth factor (TGF) β, which will suppress vascular, cardiac or renal inflammation. As a result of stimulation of damage-activated molecular pattern (DAMP) receptors, APC or DCs adopt a pro-inflammatory phenotype, migrate to secondary lymphoid organs and stimulate the maturation of T effector lymphocytes such as T helper (Th)1 which produce interferon (IFN) γ and IL-6, or Th17 which produce IL-17, leading to a vascular, cardiac, or renal inflammatory response. DAMPs stimulation could be a consequence for example of blood pressure elevation, or stimulation of pathogen-activated molecular pattern receptors, the latter in response to forms of low-grade infection, or other conditions resulting in elevated TNF-α, a consequence of genetic predisposition, high salt intake, increased endothelin (ET)-1, or activation of the renin-angiotensin II (Ang II)-aldosterone system. Formation of neoantigens, could also be a cause of activation of T effector lymphocytes leading to a role in low-grade inflammation in cardiovascular disease. HTN: hypertension; Foxp3: forhead box P3; PAMP: pathogen-activated molecular pattern. (Adapted with permission from Schiffrin E. L. The immune system: role in hypertension. Can. J. Cardiol. 2013, 29, 543-8).
els were independently associated with the development of hypertension in the follow-up study [24].

Additionally, blood pressure variability and its diurnal variations also seem to be associated with inflammation. Especially, patients with greater blood pressure variability and non-dipping nighttime pattern demonstrate increased CRP levels [31, 32]. Moreover, higher CRP levels are also present in pre-hypertensive patients and in hypertensive patients' offsprings, suggesting that low-grade inflammation, at least in some circumstances, might precede blood pressure elevations [33-35].

As for pediatric populations, cross-sectional data for children and adolescents (8-17 years old) from the National Health and Nutrition Survey have also shown that children with higher (>3 mg/l) CRP levels had higher systolic blood pressure compared to those with lower levels (≤3 mg/l), while in another study that evaluated the profile of inflammatory mediators in children with primary hypertension, hypertensive children had greater CRP, MIP-1β (Macrophage Inflammatory Protein-1β) and RANTES (Regulated on Activation Normally T-cell Expressed and Secreted) levels than controls and CRP levels were correlated with number of metabolic syndrome criteria, body mass index, carotid intima-media thickness, left ventricular mass and markers of oxidative stress [36, 37].

Likewise, CRP levels have been associated with target-organ damage. Many studies have reported an association between CRP levels and microalbuminuria in hypertensive patients [34, 40-48]. Such relation has been described even in pre-hypertension, in a study from Navarro-Gonzalez et al., where high sensitivity CRP (hsCRP) was demonstrated to be independently correlated with urinary albumin excretion and an independent risk factor for microalbuminuria. The latter implies that inflammatory processes might be part of the pathogenesis of early vascular target organ damage in pre-hypertensive individuals [34].

Furthermore, left ventricular hypertrophy (LVH) has also been related to CRP levels according to studies from Assadi et al. in children and adolescents with essential hypertension [49], while Tsai et al. reported significant increase in hsCRP among adult patients without LVH, with LVH but not proteinuria and with both LVH and proteinuria [50]. Moreover, in a study from Turak et al. hsCRP levels were significantly related to impaired echocardiographic indices of left ventricular diastolic function, independent from other factors including age, waist circumference and 24-h systolic blood pressure [51]. Similarly, studies on carotid hemodynamics and large artery stiffening on hypertensive patients report significant correlation with high or low sensitivity CRP [50, 52-55] and high hsCRP levels seem to increase the risk of stroke in hypertensive patients [56, 57].

Furthermore, Weng et al. in a prospective study concerning hypertensive patients without diabetes and vascular or renal complications at baseline, showed after a mean follow-up period of 32 ±10 months, that patients that developed diabetes had higher baseline log-hsCRP and log-hsCRP, age and baseline glucose level were found to be independent predictors for future development of diabetes. The authors suggested that there might be a link between inflammation and the pathogenesis of diabetes in hypertensive patients [58]. Finally, Ozdogan et al. reported that patients with white-coast hypertension also have higher CRP levels than normotensive patients and suggested that these patients might be of increased cardiovascular risk [59].

**CYTOKINES**

Cytokines represent a diverse group of various soluble short-acting molecules (proteins, glycoproteins and peptides) exerting a wide range of actions. They are produced and secreted in extremely low concentrations by a variety of immune (macrophages, T lymphocytes), vascular cells and adipocytes, activate specific receptors and modulate the function of many cells and tissues including immune, vascular smooth muscle and endothelial cells as well as extracellular matrix [58, 59]. Many individual cytokines are pleiotropic encompassing multiple actions, while others exert overlapping actions. They are primarily involved in host response to disease or infection and most of them are not expressed unless specifically stimulated by a noxious event [62].

They are classified into the following categories: Tumor Necrosis Factors (TNFs), Interleukins (ILs), Lymphokines and Monokines, Interferons (IFNs), Colony stimulating factors (CSFs), Transforming growth factors (TGFs), Bone morphogenetic proteins (BMPs) and Chemokines. Some cytokines, called pro-inflammatory cytokines, are produced predominately by activated macrophages and promote inflammation by acting as endogenous pyrogens, chemoattractants or by up-regulating inflammatory reaction, whereas others suppress the activity of pro-inflammatory cytokines and are involved in the down-regulation of inflammatory response exhibiting anti-inflammatory action (anti-inflammatory cytokines) [61, 63].

The importance of specific cytokines in cardiovascular disease and hypertension has been demonstrated in a number of recent studies [64]. TNF-α and IL-6 are the most studied cytokines in hypertension. Bautista et al. reported that raised TNF-α and IL-6 levels were independent risk factors for high blood pressure in apparently healthy subjects after adjustment for age, sex, BMI, family history of hypertension and the levels of the other inflammatory markers [65].

Furthermore, in a study from Mauno et al. baseline levels of IL-1β and IL-1ra were significantly higher in those individuals that developed hypertension during the follow up, providing evidence that pro-inflammation might precede hypertension [66]. Similarly Navarro-Gonzalez et al. revealed that plasma hsCRP levels and urinary TNF-α excretion were higher in high-pre-hypertensive patients compared to healthy volunteers, however among pre-hypertensive patients the inflammation markers were higher in those with microalbuminuria [32].

Moreover, serum levels of IL-6, soluble receptor of TNF-α type 1 and soluble receptor of TNF-α type 2 were found higher in patients with target organ damage than in hypertensive patients without organ damage. Increasing levels of these molecules were associated with a progressive increase in the number of organs damaged, suggesting that extensive hypertensive disease with involvement of more target organs might be associated with greater inflammatory and apoptotic activation in these patients [67]. Jastrzebski et al. also found higher levels of TNF-α in hypertensive patients with target
organ damage compared with controls and hypertensive patients without target organ damage or associated clinical condition [54].

Additionally, Mahmud et al. reported significant correlations between IL-6 and TNF-α levels and markers of arterial stiffness such as pulse wave velocity and augmentation index in hypertensive patients, however, only hsCRP was an independent predictor of pulse wave velocity and augmentation index in a multiple stepwise regression model [55].

Likewise, in a study of Naya et al. on hypertensive patients, elevated plasma IL-6 and TNF-α levels were independent predictors of coronary endothelial dysfunction, recommending that plasma IL-6 and TNF-α might be useful for identifying the high-risk subgroup of hypertensive patients with coronary endothelial dysfunction [68].

Serum levels of TNF-α and IL-6 were also increased in proportion to urinary albumin excretion rate and might play an important role in the pathogenesis and the development of hypertensive renal damage as Yu et al. suggested in a study concerning hypertensive patients [67]. In contrast, in a study from Tsioufis et al. investigating whether urinary albumin excretion was associated with markers of low-grade inflammation in hypertensive subjects, hs-CRP and not IL-18, nor soluble CD40 ligand (sCD40L), was associated to albumin-to-creatinine ratio, implying activation of different inflammatory pathways in the progression of renal and cardiovascular atherosclerotic disease [41].

Larrouse et al. found no differences in serum CRP, IL-6 and adhesion molecules (soluble intercellular adhesion molecule type 1 - sICAM-1, soluble vascular cell adhesion molecule type 1 - sVCAM-1) between salt-sensitive and salt-resistant hypertensive patients, nevertheless salt-sensitive hypertensives showed age-adjusted increased levels of p-selectin and MCP-1 [70].

Another cytokine that has been studied in patients with hypertension is osteopontin. Osteopontin exhibits pro-inflammatory action and has recently emerged as a clinically important marker since its plasma levels are elevated in atherosclerotic disease and has been shown to correlate with future cardiovascular events in patients with chronic stable angina [71, 72]. In hypertension, osteopontin levels but not IL-6, TNF-α and hsCRP levels, were higher in patients with primary aldosteronism compared to patients with essential hypertension, implying a relationship between aldosterone and inflammation [73]. Furthermore, a recent study from Stepien et al. revealed elevated osteopontin levels in hypertensive individuals in comparison to normotensives and significant correlations were observed between osteopontin levels and (CRP) and plasma glucose [74].

**ADHESION MOLECULES**

Cell adhesion molecules (CAMs) participate in several pathological conditions such as cancer and inflammatory diseases. Selectins, integrins, cadherins and immunoglobulin gene superfamily of adhesion receptors play a fundamental role in endothelial cells-leukocytes adherence and subsequent migration of white blood cells into perivascular tissue, contributing in the initiation of atherosclerotic process [75]. It has been suggested that a common feature of all major risk factors for atherosclerosis, including hypertension, is the stimulation of leukocyte chemotaxis and adhesion to endothelial cells [76]. Soluble forms of cell adhesion molecules can be detected in plasma and increased levels have been found to be associated with endothelial cell activation and inflammation [77, 78].

Several studies have reported higher soluble levels of various adhesion molecules such as e- and p-selectin, ICAM-1 and VCAM-1 in patients with essential hypertension compared to normotensive controls [78-83]. First to provide evidence were Buemi et al. who demonstrated the relationship between increased blood pressure and increased plasma levels of adhesion molecules. In their study, hypertensive patients had higher soluble levels of e-selectin, VCAM-1, and ICAM-1 than normotensives and even a short-term increase in blood pressure, induced with cold pressor test, was accompanied by a significant increase in soluble levels of those molecules not only in hypertensive but also in normotensive subjects. Authors proposed that the rise in soluble levels of the adhesion molecules was the effect of pressure increase caused by the cold pressor test on the endothelium since no significant alterations were detected in the expression of adhesion molecules studied on the surface of monocytes and lymphocytes [78].

Concurrently, DeSouza et al. in a study including older patients with uncomplicated hypertension showed a positive correlation of soluble ICAM-1 and both systolic and diastolic blood pressure, while soluble VCAM-1 was positively correlated with systolic blood pressure and age, implying a link between inflammation, endothelial dysfunction and hypertension [84].

Similarly, hypertensive patients, in a study by Parissis et al., also exhibit higher levels of various inflammatory mediators such as soluble adhesion molecules (ICAM-1, VCAM-1 and p-selectin), plasma concentrations of granulocyte-macrophage colony-stimulating factor, MCP-1, macrophage inflammatory protein-1α, RANTES, as well as plasma endothelin-1 compared to normotensive controls. Beside that, in hypertensives plasma endothelin-1 levels correlated significantly with plasma levels of soluble ICAM-1 and MCP-1 suggesting that these findings might reflect the unfavorable effects of hypertension on endothelial function [80, 85].

Additionally, Glowinska et al. in a study concerning children and adolescents with risk factors for atherosclerosis, such as obesity, diabetes and hypertension, revealed elevated concentrations of sICAM-1, sVCAM-1, and e-selectin in these subjects compared with healthy controls. Particularly, the highest concentrations of these molecules appeared in obese children with coexisting hypertension [81]. Furthermore, Chao et al. reviewed the interactions between integrins and growth factors receptors in response to the increased mechanical stress on blood vessels in hypertension. They concluded that integrins signaling contributes to vascular changes in at least two ways: either by regulating vasoconstriction and vasodilation in reaction to sensing the altered mechanical environment in the vessel wall or by participating in vascular smooth muscle cell proliferation and vascular remodeling in response to biochemical stimulators such as angiotensin II [86].
Moreover, some studies investigated adhesion molecules as prognostic marker of hypertension, while others explored their role as mediators of hypertensive vascular injury. For example, Xu et al. supported that the upregulation of junctional adhesion molecule-A (JAM-A) might be triggered by angiotensin II T1 receptor-mediated signaling preceding the stable elevation of blood pressure. These observations raise an intriguing possibility of using JAM-A as an early biomarker of pre-hypertensive state [87]. Elsewhere, Cottone et al. showed elevated soluble ICAM-1 and VCAM-1 levels in patients with essential hypertension without diabetes or echocardiographic evidence of atherosclerosis compared to normal controls and also among hypertensive patients with microalbuminuria compared to those without microalbuminuria, implying that in essential hypertension there is a very early activation of the endothelial adhesion molecules that favors atherosclerosis [88].

OTHER INFLAMMATION MARKERS

A number of novel inflammatory markers have been investigated in patients with essential hypertension, among them soluble CD40 ligand (sCD40L), human cartilage glycoprotein 39 (YKL-40), Alpha 1-microglobulin and visfatin.

Soluble CD40 ligand (sCD40L) is involved in the pathogenesis of cardiovascular risk factors associated with vascular damage and has been regarded as a molecular link between inflammation, thrombosis and angiogenesis [89]. Studies have shown that angiotensin II promotes and augments the inflammatory activation induced by CD40/CD40L ligation in human vascular cells and sCD40L levels have been found elevated in hypertensive patients, which might be useful in identifying hypertensive patients at a high risk of cardiovascular events [90, 91]. Indeed, Alioglu et al. showed that non-dippers had elevated sCD40L levels that might contribute to higher susceptibility for developing vascular damage in this hypertensive group [92]. Yuan et al. also revealed a link between sCD40/CD40L levels and hypertensive target organ damage and that might be of predictive value. In their study sCD40 levels were closely associated to the severity of hypertensive target organ damage. In contrast, it is aforementioned that patients with essential hypertension and microalbuminuria presented increased hsCRP, but not IL-18 and sCD40L levels [41].

YKL-40, a heparin and chitin binding glycoprotein, has been proposed as a novel marker of inflammation, atherosclerosis and endothelial dysfunction in neoplastic, cardiovascular and metabolic diseases [93]. In hypertensive patients, Diao et al. detected higher YKL-40 levels than normotensive controls and a positive correlation to blood pressure level but not to endothelin-1, NO and flow-mediated dilatation. Authors inferred that this novel biomarker might be used to reflect inflammation status but not endothelial function in hypertensive patients [95]. Ma et al. also showed significantly increased YKL-40 levels in essential hypertension group and further increased in those with combined microalbuminuria compared to those without microalbuminuria. However, YKL-40 levels were independently associated with parameters of arterial stiffness implying a mechanism possibly related to arterial endothelium dysfunction [95].

Alpha 1-microglobulin is an immunomodulatory protein, synthesized in liver and kidneys, that exists in blood as both free/unbound and complexed with IgA and albumin forms. Urinary excretion of alpha 1-microglobulin is increased in renal tubular dysfunction, so it is considered an index of early tubular damage [96, 97]. In newly diagnosed hypertensive, non-diabetic patients with normal renal function Vysoulis et al. observed that urinary excretion of alpha 1-microglobulin was independently associated with acute phase proteins, which might reflect the overall patients’ inflammatory status and that systolic hypertension was a major contributor to urinary excretion of alpha 1-microglobulin [98].

Finally, Gunes et al. showed that visfatin, a peptide secreted by visceral and stimulate pro-inflammatory cytokines, was higher in hypertensive patients than healthy controls. Moreover, visfatin levels were proportional to the hypertension stage as well as higher in pre-hypertensive patients than in participants with normal blood pressure [99]. In a different manner, Dogru et al. evaluated visfatin levels and reported no significant difference between young hypertensive patients and the control group. However, it is not clear whether patients’ young age affects these findings [100].

TREATMENT PERSPECTIVES

The involvement of inflammatory processes in the pathogenesis of hypertension as well as in the development of target organ damage has intrigued the scientific interest on whether current hypertensive drugs have pro- or anti-inflammatory effects and whether new drugs with proven anti-inflammatory action have any effect on modifying hemodynamics and outcomes on hypertensive patients.

Diuretics, for a long time, have remained the cornerstone of antihypertensive treatment and they were thought to have anti-inflammatory effects, by enhancing natriuresis, since salt is shown to increase the isoprostane 8-iso-prostaglandin F2α, therefore, oxidative stress in hypertensive humans [101]. Nevertheless, hydrochlorothiazide treatment did not improve neutrophil superoxide anion, MCP-1, sVCAM-1, or low-density lipoprotein oxidation in hypertensive patients after 4 weeks of treatment [102]. Additionally, Eriksson et al. suggested that the diabetogenic potential of thiazide diuretics in obese-hypertensives are based on pro-inflammatory mechanisms. In this study after 12 weeks of hydrochlorothiazide therapy, the reductions in insulin sensitivity and the ratio of subcutaneous to visceral fat, combined with an increasesin hepatic fat content and glycosylated hemoglobin, were associated with stimulation of the inflammatory marker, hsCRP [103].

Vasodilatory b-blocking agents, such as carvedilol and bisoprolol are proven to have anti-apoptotic, antioxidant and anti-inflammatory effects, whereas, non-vasodilatory agents, such as atenolol and metoprolol, do not prevent up-regulation of inflammatory and pro-thrombotic molecules and do not improve oxidative stress status in hypertensive patients [104-109].

Furthermore, vasodilatory calcium channel blockers also exhibit pleiotropic effects that are related to anti-inflammator actions. Specifically, dihydropyridines in hy-
pertinent patients inhibit cytokines (osteopontin, IL-1β, TGF-b1) synthesis and adhesion molecules (VCAM-1, ICAM-1) expression and diminish oxidative stress by reducing superoxide, peroxynitrite and isoprostanes in endothelial, vascular smooth muscle and circulating mononuclear cells [108, 110-114].

However, the most studied antihypertensive agents with proven anti-inflammatory and antioxidant effect are blockers of renin-angiotensin-aldosterone system. Angiotensin converting enzyme inhibitors (ACEi) decrease the expression of IL-6, sCD40L, adhesion molecules and selectins in patients with hypertension, improve endothelial function and suppress plasma aldosterone levels [115-117]. Besides, mineralocorticosteroid receptor blockers (MRAs) such as spironolactone and eplerenone, exhibit various pleiotropic effects including anti-inflammatory action by inhibiting multiple cytokines, chemmotactants, pro-inflammatory enzymes and growth factors along with markers of oxidative stress [118-121].

In several clinical studies, angiotensin II receptor blockers (ARBs) have been shown to reduce inflammation markers in hypertensive patients and their anti-inflammatory action seems to be superior to that of calcium channel blockers (CCB). Particularly, ARBs treatment in hypertensive patients attenuated MCP-1 gene expression and reduced hs-CRP, TNF-α, IL-6, osteopontin, sCAM-1, sCD40L and pentraxin 3 levels [102, 110, 122-125]. Beyond, the combination of the ARB-olmesartan with the CCB-amlodipine proved to be more efficient than the combination with hydrochlorothiazide, in improving metabolic status and reducing inflammatory markers in hypertensive patients with metabolic syndrome, while both combinations achieved adequate BP control, exhibiting similar anti-hypertensive action [113].

Regarding the pleiotropic effects of statins and mostly their anti-inflammatory actions, Han et al. reported significantly reduced sCD40L levels with simvastatin, losartan and combined therapy in hypercholesterolemic, hypertensive patients. Interestingly enough, the combined therapy achieved greater reduction than losartan or simvastatin alone [123]. Likewise, in a study of Gomez-Garcia et al. both treatment strategies with rosuvastatin or metformin significantly reduced inflammation and oxidative stress markers in hypertensive patients with dyslipidemia [126]. On the contrary, in a cross-over designed randomized trial on hypertensive patients without dyslipidemia, fluvastatin treatment was not found to improve endothelial function, oxidative stress or inflammation markers [125].

Finally, peroxisome proliferator-activated receptors (PPAR) agonist such as the anti-licemid drugs, fibrates and the anti-diabetic drugs, glitazones, appear to have antioxidant, anti-inflammatory and blood pressure lowering properties [126]. Notably, PPARγ agonists were shown to significantly decrease blood pressure in type 2 diabetes patients with no evidence of macrovascular disease in the PROspec-tivepioglitAzone Clinical Trial In macro Vascular Events (PRoActive) study [129]. Moreover, PPAR agonists seem to decrease inflammatory markers in hypertensive patients, along with diminishing the development of hypertension and improving vascular inflammation in angiotensin II induced hypertensive rats. They have also demonstrated renoprotective and vascular protective effect in hypertensive obese rats [130-136].

CONCLUSION

Inflammation has been recognized as an important pathophysiologial factor in hypertension. Many inflammation markers such as CRP, cytokines, and adhesion molecules have been found elevated in hypertensive patients compared to normotensives, further supporting the role of inflammation in hypertension. Moreover, they have been associated with the risk of developing hypertension in normotensive individuals, while in hypertensive patients there is a strong association with target organ damage and risk for future cardiovascular events. Furthermore, anti-hypertensive agents apart from blood pressure lowering effect, also seem to reduce inflammation markers whilst agents with proven pleiotropic effects, including statins and PPARs, seem to have favorable effects regarding inflammationin hypertensive patients, providing new insights for the treatment of hypertension and its complications.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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Inflammation Markers in Essential Hypertension

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