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The role of inflammatory biomarkers in the arterial hypertension

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Abstract

Studies on both humans and animals have found evidence of a link between inflammation and hypertension (HTN). A lower serum calprotectin level was found to be independently related to HTN. The elevated ferritin–HTN link could be mediated by fatty liver disease and insulin resistance (IR). Similarly, fibrinogen was engaged in several processes that may increase the risk of HTN which including hemostasis, coagulation, and the proliferation of smooth muscle cells in the artery wall, and others. Procalcitonin monitoring could be a useful biomarker in inflammation related to atherosclerosis and early-stage HTN. Plasminogen activator 1 (PAI-1) was not just a result of HTN but also contributes to its development. Also, the positive correlation between monocyte chemoattractant protein 1 (MCP-1) levels with blood pressure were found among smokers. The high level of pentraxin 3 (PTX3) was one of the factors of increased blood pressure. Galectin 3 (Gal-3) may contribute to the onset and progression of diastolic dysfunction-complicated HTN. Increased intercellular adhesion molecules (ICAM)/vascular cell adhesion molecule 1 (VCAM-1) ligand expression, along with a drop in soluble cell adhesion molecules (sCAMs) and endocan, points to endothelium deactivation with

lower blood pressure, which reduces the adherence of circulatory leukocytes to endothelium and, as a result, lowers the probability of atherosclerosis developing. The circulating levels of soluble VCAM-1 were substantially connected with left ventricular mass indexes (LVMIs) and were higher in uncomplicated essential hypertension (EH) patients with left ventricle (LV) hypertrophy than in those without LV hypertrophy.

Key words: arterial hypertension; biomarkers; inflammation; pathogenesis

Introduction

From epidemiological standpoint, hypertension (HTN) is one of the most important modifiable risk factors for cardiovascular disease (CVD) and premature death. It is estimated, that one-fourth of the world's adult population is hypertensive and it is likely to reach 29% by 2025 [2]. Globally, particularly in low- and middle-income countries, the prevalence and overall impact of HTN are increasing [1]. Inflammatory mechanisms that contribute to the pathophysiology of CVD and HTN. The study of how inflammation and immunological activation contribute to the onset and maintenance of HTN has attracted more attention in recent years [3].

Independent of other preexisting risk factors or poor lifestyle choices, a relationship between prehypertension and inflammatory markers [C-reactive protein (CRP), white blood cells (WBC), interleukin 6 (IL-6), tumor necrosis factor alpha (TNF-α), amyloid A, homocysteine, and fibrinogen] linked to the atherosclerotic process after studying a large sample of persons without CVD. The author's findings may have clinical implications since they imply that prehypertension may be a condition that promotes inflammation [4]. Similarly, Rabkin et al. findings point to a dynamic interaction between inflammation and HTN with dyslipidemia. Although HTN was associated with an increase in these inflammatory markers, the link conditions diabetes mellitus or metabolic syndrome cause different patterns of increases- monocyte chemoattractant protein-1 (MCP-1) was most consistently increased with HTN, CRP was most significantly increased with HTN and diabetes mellitus, and there was no correlation between interleukin-18 (IL-18) and HTN in the presence of diabetes mellitus or metabolic syndrome. In addition, statins have various effects depending on the type of inflammatory marker [5]. A large number of research

points to altered immunity and inflammation as key players in the development of HTN and as mediators of its consequences [3].

Although inflammation is well-established to be linked to HTN, it is still unclear whether inflammation is a cause or an effect of HTN. Focusing on the inflammatory response carried on by essential hypertension (EH) is becoming more and more popular. The pathophysiology and development of CVD are significantly influenced by inflammatory processes. Recent research has demonstrated that a higher risk of HTN is connected with tissue expression and plasma concentrations of several inflammatory markers and mediators.

Therefore, for the first time, this review article collectively reports the focus on the role of major biomarkers of inflammation, which were not reported before in HTN. It includes calprotectin, erythrocyte sedimentation rate (ESR), ferritin, fibrinogen, procalcitonin (PCT), plasminogen activator-1 (PAI-1), MCP-1, serum amyloid A (SAA), pentraxin 3 (PTX3), galectin 3 (Gal-3), and diagnostic value of the concentration of adhesion molecules in the pathogenesis of arterial HTN as explained in Figure 1 and 2.

To review the literature, various databases including Google Scholar, PubMed, and Science Direct were employed. The search was completed on June 10, 2022. There are many keywords such as inflammation, biomarkers, arterial HTN, and pathogenesis used. Clinical investigations could only be conducted in English. Despite supporting more recent studies, we did not set a time limit. The relevant articles' references were examined, and comparable articles were found.

Figure 1. Serum levels of major biomarkers of inflammation in hypertensive subjects. Gal-3 — galectin 3; MCP-1 — monocyte chemoattractant protein-1; PAI-1 — plasminogen activator-1; PCT — procalcitonin; PTX3 — pentraxin 3; ESR — erythrocyte sedimentation rate. Source: Designed by the authors with the help of articles

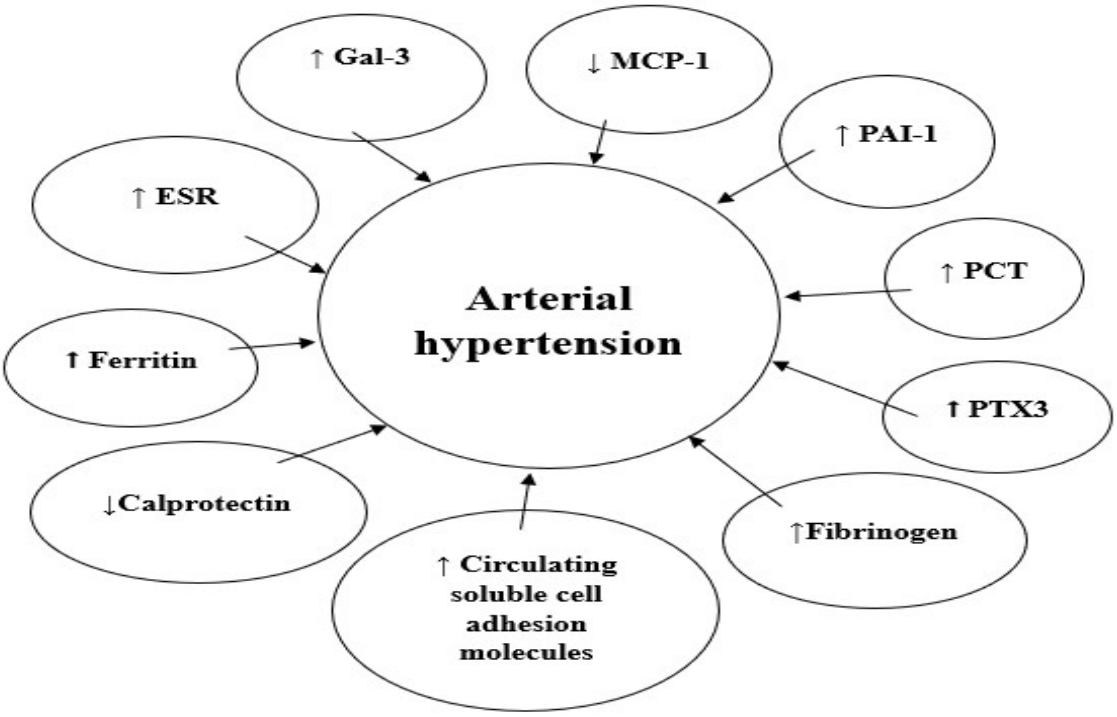
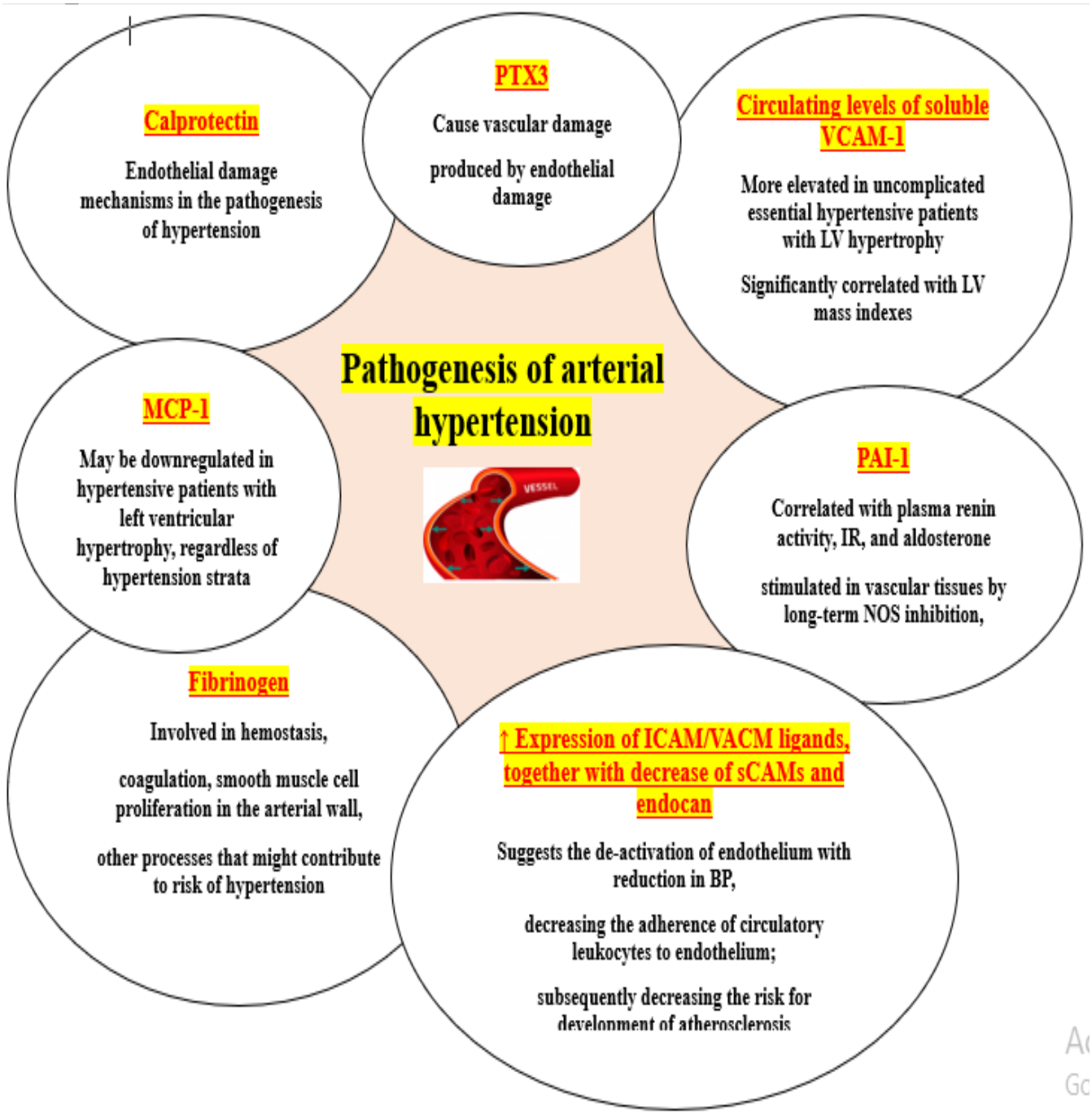


Figure 2. Overall summary of major biomarkers of inflammation's role in the pathogenesis of arterial hypertension (HTN). PTX3 — pentraxin 3; VCAM-1 — vascular cell adhesion molecule 1; LV — left ventricle; PAI — plasminogen activator; IR — insulin resistance; NOS — nitric oxide synthase; ICAM — intercellular adhesion molecules; SCAMs — soluble cell adhesion molecules; BP — blood pressure; MCP-1 — monocyte chemoattractant protein-1; Source: Designed by the authors with the help of articles



Major inflammatory biomarker in the pathogenesis of arterial hypertension

This review article focuses on the role of calprotectin, ESR, ferritin, fibrinogen, PCT, PAI-1, MCP-1, SAA, PTX3, Gal-3, and diagnostic value of the concentration of adhesion molecules as biomarkers of inflammation in arterial HTN as explained in Table 1.

Calprotectin

Calprotectin is an inflammatory marker that increases in parallel with disease activity in conditions including systemic inflammatory diseases, infection, and atherosclerosis. It has been suggested that serum calprotectin levels may be a sign of the inflammatory process in HTN, even though calprotectin was typically characterized as an acute inflammatory marker due to the endothelial damage processes involved in the pathogenesis of HTN. A lower serum calprotectin level was found to be independently related to HTN. Further comparative studies involving patients at different stages of HTN may contribute to clarifying the relationship between calprotectin and HTN. The authors conclude that molecular studies seem essential for understanding the place of calprotectin in HTN-associated inflammation, a complex process [6].

Erythrocyte sedimentation rate

The erythrocyte sedimentation rate is a surrogate marker of the acute phase reaction. During an inflammatory reaction, the sedimentation rate was affected by increasing concentrations of fibrinogen, the main clotting protein, and alpha globulins. The test mainly measures the plasma viscosity by assessing the tendency for red blood cells to aggregate and “fall” through the variably viscous plasma [7].

Mirsaeidi et al. explained that the level of systemic inflammation in sarcoidosis patients reflected by a higher ESR, and CRP could be linked with the presence of systemic hypertension (sHTN). The authors provide insight into the role of systemic inflammation in the development of sHTN as an additional complication of the disease. Moreover, suggesting the importance of a closer follow-up of blood pressure in normotensive sarcoidosis patients with elevated inflammatory markers. The study might also stimulate the conduction of further trials to assess the role of anti-

inflammatory drugs in the control and/or regression of sHTN in sarcoidosis subjects who had developed sHTN after the diagnosis of sarcoidosis [8].

Ferritin

As an acute phase reactant that may be elevated during any inflammatory or infectious condition, ferritin requires cautious interpretation in these circumstances. In a recent study, elevated ferritin levels were positively connected with the risk of metabolic syndrome and obesity. In overweight and obese people, ferritin was a measure of inflammation rather than iron status. High ferritin levels were associated with subclinical inflammation in overweight and obese individuals may conceal an underlying iron deficit since ferritin is an acute-phase reactant [9].

Numerous studies have suggested that serum ferritin levels could reflect systemic inflammation and the risk of HTN in adult men could increase due to the higher ferritin levels. The authors conclude that the prevalence of HTN increased as ferritin levels increased in individuals, especially in shift workers [10]. Another study stated that increased serum ferritin was more common in men with HTN than in controls. The metabolic abnormalities and serum ferritin were frequently positively associated, and hypertensive males with higher serum ferritin had more frequent and significant metabolic alterations than those with normal serum ferritin. Metabolic and iron data in hypertensive men with elevated serum ferritin were similar to those in insulin-resistance-associated hepatic iron overload syndrome (IRHIO) patients with HTN [11]. Additionally, Kim et al. reported that in middle-aged Korean males, serum ferritin, but not iron level was a significant predictor of HTN. The elevated ferritin–HTN link could be mediated by fatty liver disease and insulin resistance [12].

Another study has shown a positive relationship between hemoglobin (Hb) and ferritin and systolic blood pressure (SBP) and diastolic blood pressure (DBP), especially within HTN levels. Consistencies between the results of both variables (ferritin and Hb) show that iron-dependent mechanisms were involved in at least some of these favorable relationships. Older individuals and their healthcare providers should be aware of the risks of taking iron supplements without

supervision, especially if they have high blood pressure or taking antihypertensive drugs [13]. Furthermore, Hafeez et al. investigated to find a positive link between high blood pressure and mean serum ferritin levels among individuals [14].

Fibrinogen

Fibrinogen was involved in several processes that may increase the risk of HTN, including hemostasis, coagulation, the proliferation of smooth muscle cells in the artery wall, and others [15, 16]. CVD is associated with increased plasma fibrinogen. However, it is unclear if fibrinogen levels can predict the onset of HTN. Shankar et al. explained that the Atherosclerosis Risk in Communities Study's findings was supported by the data, which offer prospective epidemiological evidence of an important relationship between plasma fibrinogen level and incident HTN among men but not women [17]. The plasma fibrinogen was identified as an inflammatory marker that increases in response to mental stress. The authors discovered that whereas men did not exhibit the same pattern, women who had higher fibrinogen responses to stress had a higher risk of developing HTN in the future. Future research is necessary to confirm whether there is a sex difference in connection with HTN [18].

Letcher et al. stated that blood viscosity and blood pressure were directly correlated in normotensive and hypertensive individuals. A higher fibrinogen level and an increased hematocrit value have rheologic consequences that contribute to this association. It was unclear what causes hyperfibrinogenemia in hypertensive people [19]. Also, Leite et al. concluded that fibrinogen levels significantly increased with SBP and pulse pressure only among the elderly with metabolic syndrome or diabetes, and were particularly high among those with stage 2 HTN [20].

Fogari et al. resulted that both SBP and DBP and fibrinogen levels were not substantially correlated. Moreover, in hypertensive patients, a family history of HTN seems to exacerbate the potential of fibrinogen to cluster with other cardiovascular risk factors [21]. According to the results of another study, fibrinogen levels were significantly higher in HTN patients than in controls, and gender did not affect these levels [22].

The serum CRP and plasma fibrinogen levels were increased in hypertensive individuals and significantly linked with body mass index (BMI). Therefore, regular assessment of plasma fibrinogen and serum CRP might be a potential tool for early detection of those who were at risk for developing HTN and cardiovascular disorders [23].

Procalcitonin

Procalcitonin is a peptide containing 116 amino acids and is also known as the prohormone of calcitonin. It is a well-known prohormone of calcitonin whose concentration rises in patients with bacterial meningitis or sepsis. However, its primary site of production and its role is still unclear. [24]. In animal models, inflammation was thought to be a key factor in artery damage caused by excessive salt. Mallamaci et al. concluded that in patients with EH, a very low salt diet generates a pro-inflammatory phenotype characterized by an increase in procalcitonin and TNF-α and an opposite effect on anti-inflammatory cytokine-like adiponectin [25]. In the same context, Yavuzer et al. suggested that PCT monitoring could be a useful biomarker in inflammation related to atherosclerosis and early-stage HTN [26].

Plasminogen activator 1

Positive acute phase proteins such as PAI-1 are markedly increased under proinflammatory conditions such as acute tissue injury, sepsis, and inflammation. The primary function of PAI-1 is seen as a protective mechanism to prevent the spread of infections and encourage tissue healing [27]. In the high-risk cohort, a greater plasma PAI-1 level was specifically linked to a more than 35% higher chance of developing HTN. Peng et al. findings imply that plasma PAI-1 may influence the onset of HTN via routes other than those caused by conventional risk factors [28]. Moreover, Boe and coworkers reported that pharmacological inhibition of PAI-1 was protective against the development of HTN, cardiac hypertrophy, and periaortic fibrosis (i.e., arteriosclerosis) in mice treated with Nω-nitro-L-arginine methyl ester (L-NAME) to inhibit endothelial nitric oxide synthase (eNOS) [29]. The levels of PAI-1 in the hypertensive participants were correlated with plasma renin activity, insulin resistance, and aldosterone

(ALDO). The data suggested that ALDO may play a significant role in explaining the heterogeneity of PAI-1 levels in specific hypertensive people [30].

HTN and perivascular fibrosis have been linked to long-term inhibition of nitric oxide synthase (NOS). The production of PAI-1 was stimulated in vascular tissues by long-term NOS inhibition, and recent research showed that PAI-1 might help in the development of fibrosis after chemical or ionizing injury. Based on these observations, Kaikita et al. hypothesized that PAI-1 might influence the vascular response to long-term NOS inhibition by N^{ω}-nitro-L-arginine methyl ester (L-NAME). As a result, in the presence of long-term NOS inhibition, PAI-1 deficiency alone was adequate to guard against the structural vascular alterations that accompany HTN. A new treatment approach for the prevention of arteriosclerotic CVD may be provided by directly inhibiting vascular PAI-1 activity [31].

The probability of developing HTN was enhanced by $PAI\text{-}1_{act}$ and the 4G/4G (vs. the 5G/5G) genotype. Furthermore, both brachial and central BP were prospectively linked with $PAI\text{-}1_{act}$. Central obesity played a role in mediating these relationships. The research supported the idea that PAI-1 was not just a result of HTN but also contributes to its development [32]. To evaluate the relationship between plasma PAI-1 and angiotensin II (Ang II) changes during treatment with imidapril and candesartan in hypertensive patients with metabolic syndrome. As a result, the authors explained that candesartan elevated plasma PAI-1 and Ang II levels whereas imidapril decreased them. This shows that the various effects of angiotensin-converting enzyme inhibitors and Ang II blockers on Ang II production contribute to their various effects on fibrinolysis [33]. Moxonidine, an imidazoline I1-receptor agonist, a novel centrally acting antihypertensive drug, dramatically lowers urine albumin excretion as well as thrombomodulin and PAI-1 levels in hypertensive patients with microalbuminuria. According to these preliminary findings, renal function and endothelium homeostasis (maintenance of hemostatic balance) were positively affected [34].

Monocyte chemoattractant protein 1

MCP-1 (CCL2) is one of the key chemokines that regulate the migration and infiltration of monocytes/macrophages [35]. Ritter et al. observed that MCP-1 levels were identical in resistant

hypertension (RHTN) and HTN subjects but decreased in hypertensive patients with left ventricular hypertrophy (LVH). The authors' findings suggest that MCP-1 levels may be downregulated in hypertensive patients with left ventricular hypertrophy, regardless of HTN strata [36]. In the same way, Komiyama et al. reported a positive correlation between MCP-1 levels with blood pressure among smokers. Long-term smokers with high blood pressure may be more susceptible to plaque rupture at atherosclerotic lesion sites [37].

Serum amyloid A

Acute-phase reactant serum amyloid A plays an important role in acute and chronic inflammation and is used in clinical laboratories as an indicator of inflammation [38]. Furthermore, Stettler et al. reported a link between the inflammatory markers, serum amyloid A, CRP, and retinal microvascular characteristics in hypertensive people with and without type 2 diabetes. Inflammatory mechanisms were implicated in retinal microvascular dysfunction differently in diabetics versus nondiabetic hypertensive people [39].

Pentraxin 3

PTX3 is a unique and sensitive marker linking inflammation with CVD since it is produced and secreted by the majority of cell compartments involved in the initiation and development of CVD. Elevated plasma levels of PTX3 in elderly HTN individuals are a strong predictor of frailty because it plays a role in several molecular processes that cause vascular damage. Various clinical disorders affecting the cardiovascular system cause the quantity of circulating PTX3 to increase. Blood vessels generate high amounts of PTX3 during inflammation [40–43].

Carrizzo et al. discussed the acute-phase protein PTX3's direct contribution to cardiovascular homeostasis for the first time, along with how it affects experimental models of vascular function and blood pressure. PTX3, P-selectin, and MMP-1 may be potential biomarkers for the prognosis of the development of vascular dysfunction in hypertensive patients, according to data gathered from human studies. As P-selectin and MMP-1 were downstream molecules of the signaling pathway started by PTX3, these biomarkers were connected. To slow the development of high

blood pressure, monitoring these proteins may thus become a critical part of a novel preventative strategy [44]. Hypertensive patients had elevated PTX3 levels. Blood pressure was raised by the independent marker PTX3 without the help of other biochemical or inflammatory indicators. The authors believed that elevated levels of PTX3 in newly diagnosed hypertension patients were produced by endothelial damage in these individuals. PTX3 levels were explored in many research as an endothelial injury marker, but they were not regularly employed [45].

Galectin 3

Galectins are a class of multifunctional, evolutionarily conserved glycan-binding proteins. Over the past ten years, more and more research resources have been devoted to understanding them. The essential biological mediators known as galectins work either intracellularly or extracellularly to monitor alterations on the cell surface during critical biological processes such as cellular communication, inflammation, development, and differentiation [46]. Gal-3 has been connected to fibrogenesis, myofibroblast proliferation, ventricular remodeling, and inflammation for more than ten years [47].

Gal-3 could be linked to the onset and development of diastolic dysfunction-complicated HTN. However, following treatment, its concentration sharply declines. Its concentration increases with the grade of cardiac function. As a result, the level of Gal-3 before treatment may be used as an indicator of treatment effectiveness [48]. Ang II type 1 receptor gene analysis revealed that the C allele predominated in patients with EH and cardiac hypertrophy. Gal-3 and brain natriuretic peptide (BNP) levels were greater in them. Gal-3 and BNP threshold levels for the diagnosis of EH with cardiac hypertrophy were assessed in male residents of the Podillya region of Ukraine [49].

Diagnostic value of the concentration of adhesion molecules (L-selectin, E-selectin, P-selectin, integrins VCAM-1 and others)

Inflammatory factors have a major role in the consequences of HTN, such as coronary atherosclerosis and thrombosis. Inflammatory molecules including endothelial selectin (E-selectin), platelet selectin (P-selectin), ICAM-1, VCAM-1, and platelet endothelial cell adhesion molecule 1 (PECAM-1) were compared in subjects with newly diagnosed HTN who had no

secondary cause to their HTN to normotensive healthy individuals. As compared to controls median of sE-selectin, sP-selectin, and sICAM-1 were significantly elevated in hypertensive subjects. A significant negative correlation was observed between sP-selectin and sPECAM-1 with age in the HTN group. HTN may increase the expression of certain CAMs while younger hypertensives in addition were also at increased risk of atherothrombosis [50]. CVD development is linked to increased levels of circulating soluble cell adhesion molecules. The authors investigated the possibility that older men with uncomplicated EH had greater circulating levels of soluble cell adhesion molecules, which could contribute to the population's elevated risk of atherosclerosis. DeSouza et al. concluded for the first time that soluble CAM levels were increased in older men with uncomplicated EH. When compared to normotensive peers of the same age, body composition, and metabolic profile, the circulating levels of both sICAM-1 and sVCAM-1 were considerably greater in older, sedentary hypertensive individuals [51].

The increased expression of ICAM/VACM ligands, along with a decrease in sCAMs and endocan, points to the deactivation of endothelium with lower blood pressure, which reduces the adherence of circulatory leukocytes to endothelium and, as a result, lowers the risk for the development of atherosclerosis [52]. Similarly, Cottone et al. demonstrated that the activation of endothelial adhesion molecules occurs very early in EH, favoring atherosclerosis [53].

One of the components of the tight junction between adjacent endothelial cells is junctional adhesion molecule 1 (JAM-1). Waki et al.’s findings imply that JAM-1 expression was elevated throughout the body in the spontaneously hypertensive rat relative to the WKY rat and that this was not a result of hypertension. JAM-1 appears to play a unique prehypertensive role in the brain stem by increasing arterial pressure when expressed in the nucleus tractus solitarii [54].

Initial stages in the development of hypertension include monocyte and adhesion infiltration into the vascular subendothelium. Leukocyte recruitment and adhesion have been linked to many cardiac disorders through the endothelial ICAM-1. Lang et al. were the first to demonstrate that ICAM-1 overexpression contributes to the mice's HTN caused by Ang II. ICAM-1 expression was elevated in the aorta after an Ang II infusion, which encourages monocyte adhesion to endothelial cells (EVs) and subsequent transendothelial migration. These alterations cause vascular remodeling, dysfunction, and HTN by causing a significant amount of proinflammatory cytokines and reactive oxygen species (ROS) to be produced [55].

In the intramyocardial arterioles, pressure overload led to ICAM-1 expression and perivascular macrophage accumulation. ICAM-1-mediated macrophage accumulation in pressure-loaded hearts has been linked to the onset of cardiac fibrosis via TGF-β induction and fibroblast activation [56]. Type 2 diabetes and HTN both frequently exhibit endothelial dysfunction. It was still unclear if blood pressure fluctuation affects serum levels of VCAM-1 and ICAM-1. A better understanding of the mechanisms causing endothelial dysfunction by examining the relationship between serum ICAM-1 and VCAM-1 and 24-hour ambulatory blood pressure fluctuation in type 2 diabetes patients and controls. By increasing the amounts of circulating adhesion molecules, elevated 24-hour ambulatory BP fluctuation might cause endothelial activation [57].

Another study showed that spontaneously hypertensive rats (SHR) with renal injury expressed more ICAM-1 in the kidneys, suggesting that inflammation might contribute to hypertensive renal damage [58]. Tissue-specific upregulation of ICAM-1 expression in spontaneously hypertensive rats. The involvement of inflammation in the kidneys may be due to proteolytic cleavage of ICAM-1's extracellular domain and accumulation in kidney glomeruli [59]. According to Kuroda et al. the circulating levels of soluble VCAM-1 was substantially connected with LV mass indexes and were higher in uncomplicated EH patients with LV hypertrophy than in those without LV hypertrophy [60].

Table 1. Summary of studies which reported the major biomarkers of inflammation in the arterial hypertension (HTN)

First author	**Year of publication**	**Biomarkers of inflammation**	**The main finding in the pathogenesis of arterial HTN**	**Ref.**
Bayrakci et al.	2022	Calprotectin	A lower serum calprotectin level was found to be independently related to HTN	[6]
Mirsaeidi et al.	2016	ESR, CRP	Level of systemic inflammation in sarcoidosis patients — reflected by a higher erythrocyte sedimentation rate, CRP may be associated with the	[8]

			presence of sHTN	
Lee et al.	2018	Ferritin	The prevalence of HTN increased as ferritin levels increased in individuals, especially in shift workers	[10]
Piperno et al.	2002	Ferritin	In hypertensive men with the increased serum ferritin, metabolic and iron data were similar to those of IRHIO patients with HTN	[11]
Kim et al.	2012	Ferritin	In middle-aged Korean males, serum ferritin, but not iron level, was a significant predictor of HTN	[12]
Jamshidi-Naeini et al.	2019	Ferritin	Evidence of the positive association between Hb and ferritin with SBP and DBP, particularly within HTN ranges	[13]
Hafeez et al.	2022	Ferritin	A positive association between the mean serum ferritin levels and high blood pressure among the study participants	[14]
Shankar et al.	2006	Fibrinogen	Data provide prospective epidemiological evidence of an essential link between plasma fibrinogen level and incident HTN among men but not among women, a finding consistent with that observed in the Atherosclerosis Risk in Communities Study	[17]
Steptoe et al.	2016	Fibrinogen	Women with greater fibrinogen responses to stress were at raised risk of future HTN, but the same pattern was not observed in men	[18]
Letcher et al.	1981	Fibrinogen	This relationship is, in part, due to the rheologic effects of an elevated	[19]

			fibrinogen level and an increased hematocrit value. The basis for hyperfibrinogenemia in hypertensive patients is unclear	
Leite et al.	2011	Fibrinogen	Fibrinogen levels significantly increased with SBP and pulse pressure only among the elderly with metabolic syndrome or diabetes and were particularly high among those with stage 2 HTN	[20]
Fogari et al.	1994	Fibrinogen	Both SBP and DBP and fibrinogen levels were not substantially correlated	[21]
Eldour et al.	2016	Fibrinogen	A significant increase in fibrinogen levels in hypertensive patients compared to control, while gender does not affect the level of fibrinogen	[22]
Yeldu et al.	2018	Fibrinogen, CRP	Serum CRP and plasma fibrinogen levels were elevated in hypertensive subjects and positively correlated with BMI	[23]
Mallamaci et al.	2013	PCT	In patients with EH, a very low salt diet generates a pro-inflammatory phenotype characterized by an increase in PCT and TNF-α and an opposite effect on an anti-inflammatory cytokine-like ADPN	[25]
Yavuzer et al.	2016	PCT	PCT monitoring may be a useful biomarker in inflammation related to	[26]

			atherosclerosis and early-stage HTN	
Peng et al.	2017	PAI-1	A higher level of plasma PAI-1 was associated with over 35% increased risk of developing HTN in high-risk population	[28]
Boe et al.	2013	PAI-1	Pharmacological inhibition of PAI-1 was protective against the development of HTN, cardiac hypertrophy, and periaortic fibrosis (i.e., arteriosclerosis) in mice treated with L-NAME to inhibit eNOS	[29]
Srikumar et al.	2002	PAI-1	Plasma renin activity, IR, and ALDO all correlate with PAI-1 levels in the hypertensive subjects	[30]
Kaikita et al.	2001	PAI-1	Suggest that PAI-1 deficiency alone was sufficient to protect against the structural vascular changes that accompany HTN in the setting of long-term NOS inhibition	[31]
Jacobs et al.	2019	PAI-1	The likelihood of developing hypertension was enhanced by PAI-1_{act} and the 4G/4G genotype (*vs*. the 5G/5G genotype)	[32]
Krespi et al.	1998	PAI-1	The moxonidine, an imidazoline I1-receptor agonist, a novel centrally acting antihypertensive drug, dramatically lowers urine albumin excretion as well as thrombomodulin and PAI-1 levels in hypertensive patients with microalbuminuria	[34]
Ritter et al.	2017	MCP-1	A possible downregulation in MCP-1 levels in hypertensive individuals with LVH, regardless of HTN strata	[36]

Komiyama et al.	2018	MCP-1	The MCP-1 concentration was positively correlated with blood pressure among smokers.	[37]
Stettler et al.	2009	SAA, CRP	A link between the inflammatory markers including serum SAA, CRP and retinal microvascular characteristics in hypertensive people with and without type 2 diabetes	[39]
Carrizzo et al.	2015	PTX3	Data show for the first time a direct role of PTX3 on vascular function and blood pressure homeostasis, identifying the molecular mechanisms involved	[44]
Parlak et al.	2012	PTX3	The high level of PTX3 was one of the factors of increased blood pressure	[45]
Dong et al.	2020	Gal-3	Gal-3 may contribute to the onset and progression of diastolic dysfunction-complicated HTN	[48]
Ruzhanskaya et al.	2018	Gal-3	Gal-3 and BNP threshold levels for the diagnosis of EH with cardiac hypertrophy were assessed in male residents of the Podillya region of Ukraine	[49]
Shalia et al.	2009	CAMs, E-selectin, P-selectin, ICAM-1, VCAM-1 and PECAM-1	The study explains inflammatory molecules such as CAMs; E-selectin, P-selectin, ICAM-1, VCAM-1 and PECAM-1 were analyzed in subjects newly diagnosed with HTN with no secondary cause against normotensive healthy individuals	[50]
DeSouza et al.	1997	Circulating	Older men with uncomplicated EH	[51]

		sCAMs	have greater levels of circulating sCAMs	
Tadzic et al.	2013	sCAMs, ICAM/VCAM ligands	The increased expression of ICAM/VACM ligands, together with the decrease of sCAMs and endocan suggests the de-activation of endothelium with the reduction in BP, decreasing the adherence of circulatory leukocytes to endothelium; subsequently decreasing the risk for development of atherosclerosis	[52]
Cottone et al.	2007	ICAM-1, VCAM-1	Findings show that in EH there was very early activation of endothelial adhesion molecules favoring atherosclerosis	[53]
Waki et al.	2007	JAM-1	When JAM-1 was expressed in the nucleus tractus solitarii, it raises arterial pressure which suggesting a novel prehypertensive role for this protein within the brain stem	[54]
Ciobanu et al.	2019	ICAM-1, VCAM-1	By increasing the amounts of CAMs, elevated 24-hour ambulatory BP fluctuation may cause endothelial activation	[57]
Zhang et al.	2012	ICAM-1	Showed that spontaneously hypertensive rats with renal injury expressed more ICAM-1 in the kidneys, suggesting that inflammation may contribute to hypertensive renal damage	[58]
Tong et al.	2011	ICAM-1	Tissue-specific upregulation of ICAM-1 expression in **SHRs**	[59]

			{spontaneously hypertensive rats???}	
Kuroda et al.	2001	sVCAM-1	Circulating levels of sVCAM-1 were substantially connected with LVMIs and were higher in uncomplicated EH patients with LV hypertrophy than in those without LV hypertrophy	[60]

ESR —1 erythrocyte sedimentation rate; CRP — C-reactive protein; sHTN — systemic hypertension; IRHIO — insulin-resistance-associated hepatic iron overload syndrome; Hb — hemoglobin; SBP — systolic blood pressure; DBP — diastolic blood pressure; BMI — body mass index; EH — essential hypertension; PCT — procalcitonin; TNF-α — tumor necrosis factor alpha; **ADPN — adiponectin????;** PAI-1 — plasminogen activator-1; L-NAMEN — ω-nitro-L-arginine methyl ester; eNOS — endothelial nitric oxide synthase; IR — insulin resistance; ALDO — aldosterone; MCP-1 — monocyte chemoattractant protein 1; LVH — left ventricular hypertrophy; SAA — serum amyloid A; PTX3 — pentraxin 3; Gal-3 — galectin 3; BNP — brain natriuretic peptide; CAMs — cell adhesion molecules; ; sCAMs — soluble cell adhesion molecules; E-selectin — endothelial selectin; P-selectin — platelet selectin; ICAM-1 — intercellular cell adhesion molecule 1; VCAM-1 — vascular cell adhesion molecule 1; PECAM-1 — platelet endothelial cell adhesion molecule; JAM-1 — adjacent endothelial cells is junctional adhesion molecule-1; LVMI — left ventricular mass index

Conclusion

This review article concludes that biomarkers of inflammation play a significant role in the pathogenesis of arterial HTN as presented in Figure 2. The literature has suggested that blocking inflammatory pathways could be helpful for the prevention of the development of HTN which ultimately controls the high prevalence of cardiovascular-related diseases in which inflammation is also a risk factor. The assessment of these biomarkers may affect the particular pharmacologic reactions and the clinical result of individuals with arterial HTN. Moreover, treatment strategies that goal to reduce blood pressure and inhibit the inflammatory response may have extra clinical

advantages. The potential advantages of inflammation suppression in the treatment of arterial HTN, however, need to be determined by more randomized research.

Conflict of interest

The authors declare that they have no conflict of interest.

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Ethical standards

The manuscript does not contain clinical studies or patient data.

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