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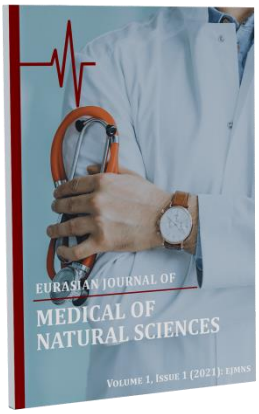

IMPACT OF CYTOKINES ON THE ONSET AND PROGRESSION OF ARTERIAL HYPERTENSION

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ABSTRACT

Arterial hypertension (AH), a prevalent chronic condition, is marked by consistently elevated blood pressure. Beyond the primary mechanisms contributing to the development of hypertension—such as activation of the sympathetic nervous system, disturbances in the renin-angiotensin-aldosterone system, endothelial dysfunction, heightened vascular reactivity, and vascular remodeling—inflammation is also thought to play a role in the disease's formation. This review delves into the role of cytokines in the pathogenesis of AH, examining how they interact with the body's blood pressure regulatory systems.

Introduction. Small protein molecules known as cytokines are released by immune cells that have been activated. They play a crucial role in mediating intercellular communication in both normal and pathological body processes. With continued research into the receptors for these cytokines, the genes that produce them, and the mounting body of knowledge regarding the molecular dynamics of ligand-receptor interactions, the list of identified cytokines is constantly growing. Simultaneously, there is an increasing interest in the investigation of cytokines in diverse pathological states, with their analysis being useful for comprehending etiology, gauging the severity of disease, and determining therapy efficacy. There has been a noticeable increase in conversations in the past few years on how these inflammatory mediators contribute to the development of arterial hypertension (AH).

Relevance. One of the most common multifactorial diseases, arterial hypertension (AH) affects approximately one-third of the adult population worldwide, with a prevalence of 31.5% in low- and middle-income nations and 28.5% in high-income countries. Because it increases the likelihood of major complications such myocardial infarction, stroke, renal failure, vascular thrombosis, and eye injury, its relevance is increased. The World Health Organization estimates that AH causes around 7.1 million deaths per year.

Over 90% of instances of hypertension are classified as essential arterial hypertension, which is defined by an unknown origin. This type of hypertension is frequently inherited, indicating a group of illnesses originating from metabolic problems with a hereditary basis. Environmental variables have the power to alter clinical phenotypes, affecting the degree and timing of blood pressure increase.

Genetic factors that interfere with the kidneys' regulation of water-salt metabolism are associated to the pathophysiology of AH. The sympathetic nervous system's activation and the renin-angiotensin-aldosterone system's disruption are two important pathways in the development of hypertension. Vascular remodeling, enhanced vascular reactivity, and endothelial dysfunction are becoming recognized as contributing factors to high blood pressure rather than merely effects. Furthermore, decreased vascular flexibility has been connected to isolated systolic hypertension in older persons.

Although it's still unclear whether inflammation causes or results from hypertension, emerging data suggests a link between the two conditions.

Target of the present study is to determine the role of cytokines in the formation of hypertension according to the review of world literature.

Results and discussions: *Inflammation and arterial hypertension.* The body's defensive response to an injury or the entry of infectious organisms is inflammation. This is a multi-step procedure that involves the release of the starting substance, migration of inflammatory cells to the damaged tissues, and healing of the wound. Phagocytic cells of the innate immune system (APCs, or antigen-presenting cells) and highly specialized T cells of the adaptive immune system interact during inflammation. T cell polarization and function can be altered by cytokines generated by APC and other cells inside the inflammatory center [6].

TLR (Toll-like receptor) ligands, cytokines, nitric oxide, superoxide, and other chemicals control the development of chemokines and vascular adhesion molecules, which let T cells enter target tissues. Nonspecific symptoms like elevated C-reactive protein (CRP) or tissue macrophage presence are frequently linked to the inflammatory process in cardiovascular disorders [7]. Acute phase protein CRP is implicated in innate immune responses, phagocytosis, and complement system activation [8]. It is believed that CRP causes endothelial cells to express intracellular adhesion molecules (ICAM-1) and vascular cell adhesion molecules (VCAM1) [9], as well as monocytes to release pro-inflammatory cytokines such as interleukin-6 (IL-6), interleukin-1 beta (IL-1β), and tumor necrosis factor alpha (TNF-α) [7], whose effects promote further inflammation. as an increase in C-reactive protein (CRP) or the presence of macrophages in tissues [7].

Acute phase protein CRP is implicated in innate immune responses, phagocytosis, and complement system activation [8]. as an increase in C-reactive protein (CRP) or the presence of macrophages in tissues [7]. It is assumed that CRP stimulates monocytes to release pro-inflammatory cytokines such as interleukin-6 (IL-6), interleukin-1 beta (IL-1β), and tumor necrosis factor alpha (TNF-α) [7]. Additionally, it stimulates endothelial cells to express intracellular adhesion molecules (ICAM-1) and vascular cell adhesion molecules (VCAM1) [9]. Acute phase protein CRP is implicated in innate immune responses, phagocytosis, and complement system activation [8]. Presumably, CRP causes monocytes to generate pro-inflammatory cytokines such interleukin-1 beta (IL-1β) and interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α) [7], as well as endothelial cells to expression of intracellular adhesion molecules (ICAM-1) and vascular cell adhesion molecules (VCAM1) [9], whose effects promote further inflammation.

It is thought that CRP is an inflammatory marker linked to hypertension. Numerous clinical studies that show elevated CRP in hypertension patients' blood plasma have

corroborated this association [10, 11]. Furthermore, compared to patients with normotension, those with a propensity to raise blood pressure typically had greater blood plasma levels of C-reactive protein [12]. The part cytokines play in arterial hypertension development. The significance of the quantitative expression of cytokines in blood pressure regulation and the pathogenesis of arterial hypertension is still poorly understood, despite substantial progress in understanding the role of inflammatory cytokines in the development of cardiovascular diseases [13].

Hypertonic stimuli may facilitate the formation of activated T lymphocytes in the kidneys and perivascular adipose tissue, according to a theory put forth by Harrison and associates [7]. Activated T-lymphocytes release cytokines in these areas that impact nearby vascular cells as well as the renal tubule epithelium. According to this theory, further research has confirmed that T-lymphocytes and other inflammatory cells release cytokines, which may be linked to hypertension. Research has indicated that individuals with arterial hypertension had greater blood plasma levels of cytokines, such as TNF-α [17], IL-1 [16], and IL-6 [14, 15], than patients with normotensive conditions. It is well established that the pro-inflammatory cytokines TNF-α and IL-6 interact with blood pressure regulating systems such the sympathetic nervous system and renin-angiotensin system. The sympathetic nervous system stimulates the release of pro-inflammatory cytokines, and sympathetic nerves may be the source of their production [18].

Furthermore, there is experimental evidence that pro-inflammatory cytokines activate the sympathetic nervous system [18]. Angiotensin II activates nuclear factor-kB and the monocytic chemoattractant protein-1 and increases the synthesis of TNF-α and IL-6 [13, 19, 20]. Additionally, angiotensin II raises the synthesis of reactive oxygen species, which contribute to inflammation and include hydrogen peroxide [19, 20]. Angiotensin II activates nuclear factor-kB and the monocytic chemoattractant protein-1 and increases the synthesis of TNF-α and IL-6 [13, 19, 20]. Additionally, angiotensin II raises the synthesis of reactive oxygen species, which contribute to inflammation and include hydrogen peroxide [19, 20]. Angiotensin II stimulates nuclear factor-kB and the monocytic chemoattractant protein-1, as well as increases the creation of TNF-α and IL-6 [13, 19, 20]. Angiotensin II also increases the production of reactive oxygen species, including hydrogen peroxide, which are also involved in the inflammatory process [19, 20].

Furthermore, it has been demonstrated that elevated blood pressure in experimental animals with AH is correlated with plasma levels of pro-inflammatory cytokines [21]. For instance, increasing plasma levels of TNF-α in pregnant rats increased blood pressure and renal vascular resistance, according to reports by Alexander and colleagues [22] and LaMarca and his group [21]. Orshal and Khalil [23] found comparable effects when IL-6 was administered into pregnant rats for five days.

The role of endogenous IL-6 in the development of angiotensin II-induced AH was investigated by Li and colleagues [24]. Male C57BL6 and IL-6 deletion mice were housed in metabolic cages with biotelemetry devices implanted to continuously regulate their blood pressure and metabolism in response to chronic angiotensin II-induced hypertension. A considerable increase in plasma levels of IL-6 was seen in wild-type mice suffering from chronic angiotensin-II hypertension. This study's key finding is that the concentration of IL-6

has a substantial impact on hypertension brought on by a long-term rise in angiotensin II. After receiving angiotensin II infusion for two weeks, the mean arterial pressure of IL-6 knockout mice was considerably lower than that of wild-type mice (~30 mmHg). These findings unequivocally show how the quantitative content of IL-6 mediates the angiotensin II-induced chronic hypertensive response.

Additionally, the research demonstrated that this was not post-angiotensin II hypertension and that the variation in blood pressure levels between the groups occurred prior to urinary albumin excretion. These findings imply that IL-6 plays a role in angiotensin II-induced hypertension through mechanisms that are not dependent on angiotensin II-induced renal damage. Etanercept is a TNF-α antagonist that decreases blood pressure in animals with chronic autoimmune inflammation [26], avoids vascular dysfunction and reduces angiotensin II-related hypertension [25], and lowers fructose-induced BP. TNF-α antagonists can occasionally stop target organ damage without reducing blood pressure. Etanercept, for instance, decreases albuminuria and renal inflammation in hypertensive transgenic rats [28] and protects kidney damage in saline-dependent hypertension without reducing blood pressure [27]. Angiotensin II-induced hypertension that is not salt-sensitive is also mediated by interleukin-6 [29].

It is known that IL-17, a pro-inflammatory cytokine, has a role in the development of AH. Th-17 cells, a subset of CD4+ cells, generate this cytokine. Numerous illnesses, such as psoriasis, inflammatory bowel disease, rheumatoid arthritis, and inflammatory airway diseases are associated with IL-17 [30]. Moreover, CD8+ cells, neutrophils, and natural killer cells all produceIL-17 [7]. Although IL-17-/-mice do not sustain hypertension, the rise in blood pressure in these mice was found to be comparable to that of wild-type mice. Furthermore, IL-17-/-mice did not exhibit the rise in superoxide generation and fall in endothelium-dependent vasodilation seen in wild-type mice. IL-17 promotes chemotaxis of other inflammatory cells by stimulating the release of chemokines [31]. Accordingly, vascular accumulation of leukocytes (including T cells) induced by angiotensin II was found to be markedly reduced in IL-17 −/− mice. Thus, IL-17 can contribute to the vascular mechanisms of AH not only by its direct involvement, but also by attracting other inflammatory cells to the perivascular tissue.

The role of T-regulatory cells and IL10 in the development of hypertension. Regulatory T cells (Tregs) are a subset of CD4+ cells that, in addition to Th-17 cells, are distinct from Th-1 and Th-2 subpopulations. These cells, which are essential for preserving self-tolerance, are identified by the surface expression of CD25 and the transcription factor Forkhead (FoxP3) [32]. When FoxP3 is removed from these cells genetically, it results in severe and deadly lymphoproliferative diseases [33]. According to recent research, Tregs can protect against hypertension. According to Kwaken et al., adoptive transplantation of these cells contributes to angiotensin II-induced heart damage but has no effect on the angiotensin II-dependent hypertensive response. Tregadoptive transfer lowers chronic angiotensin II-induced hypertension-related heart inflammation, hypertrophy, and fibrosis [34].

Rats with the Dahl salt sensitive (SS) genome on Brown Norway rat strain (SSBN2) chromosome 2 were investigated by Wiel and associates [35]. It is well known that chromosome 2 has loci for quantitative features of hypertension in addition to genes linked to

inflammation and hypertension. Comparing SSBN2 rats to Dahl SS rats, the authors discovered that the former had milder hypertension, fewer inflammatory cells in the aorta, and less noticeable vascular hypertrophy. Additionally, they demonstrated that, in comparison to Dahl SS mice, these animals' aortas included more Treg cells, as seen by an increase in FoxP3b mRNA. Treg cells secrete IL-10, a significant anti-inflammatory cytokine. It was discovered that SSBN2 rat Tregs produced more IL10 than Dahl SS rat Tregs.

According to the authors' findings, Tregs are crucial in lowering high blood pressure and preventing organ damage in SSBN2 mice. Dieden et al. discovered that angiotensin II incubation caused carotid endothelial dysfunction in IL-10 −/− mice, but did not harm endothelium-dependent arterial vasodilation in normal mice, which is consistent with the protective role of IL-10 [36]. Additionally, these researchers demonstrated that angiotensin II elevates the generation of vascular superoxide in IL-10 −/mice, but not in animals of the wild type. however in normal animals, it does so without impairing endothelium-dependent arterial vasodilatation [36]. Additionally, these researchers demonstrated that angiotensin II elevates the generation of vascular superoxide in IL-10 −/mice, but not in animals of the wild type. however in normal animals, it does so without impairing endothelium-dependent arterial vasodilatation [36]. Additionally, these researchers demonstrated that angiotensin II elevates the generation of vascular superoxide in IL-10 −/mice, but not in animals of the wild type.

Cytokines and endothelial dysfunction in arterial hypertension. Endothelial dysfunction is another way that inflammation may play a role in the development of hypertension. The layer of cells that lines the inside of blood arteries and is responsible for controlling vascular tone is known as the endothelium. Endothelial nitric oxide synthase (eNOS) produces nitric oxide (NO), a signaling molecule that is crucial for controlling vasodilation. Vascular smooth muscles relax and expand as a result of endothelial cells releasing NO [37]. Endothelial dysfunction typically shows up as a disruption of endothelium-dependent vasodilation because of an imbalance between vasoconstrictors and vasodilators. This can lead to an increase in systemic vascular resistance and the development of hypertension [38]. As was previously discovered, inflammation inhibits the expression of NO-synthase. For instance, by destabilizing eNOS mRNA, CRP [39] and TNF [40] reduce the generation of NO, but TNF inhibition in humans increases endothelial vasodilation [41]. It has been shown that IL17 causes endothelial dysfunction via phosphorylating eNOS's inhibitory residue, threonine 495, through the activation of Rho kinase [42].

It's crucial to remember that healthy endothelium inhibits leukocyte adhesion in a NO-dependent manner, among other anti-inflammatory functions [43]. Leukocyte adhesion molecules and chemokines, such as monocyte chemotaxis protein 1 (MCP-1) are more abundantly expressed when eNOS activity is inhibited [44]. Therefore, vascular inflammation may be made worse by endothelial dysfunction linked to elevated cytokine expression, which may then lead to hypertension.

Conclusion. Our knowledge of the involvement of inflammatory process indicators in the etiology of arterial hypertension (AH) is being expanded by the investigation of these markers in this condition. The inflammatory process in AH is associated with notable increases in markers of inflammation such as C-reactive protein (CRP), tumor necrosis factor-

alpha (TNF-α), interleukins (IL-1, IL-6), and their interactions with blood pressure regulatory systems, such as the sympathetic nervous and renin-angiotensin systems, and endothelial dysfunction.

Studies on humans and animal models have both proven the significance of cytokines in inflammation associated to hypertension. According to one theory, immune system activation and inflammation may be reactions to even slight rises in blood pressure, which are frequently regarded as harmless. Furthermore, it is thought that the clinical state known as "prehypertension" may serve as a precursor to more severe forms of hypertension.

Novel pathogenetic treatments for arterial hypertension can be developed through an understanding of the immunological systems that underlie the condition's development. It is imperative to acknowledge that a multitude of cytokines exhibit comparable biological effects, and concentrating just on renowned cytokines may not accurately depict the intricacies of cytokine regulation. Additionally, certain cytokines can interact with the receptor elements that make up such receptor complexes.

By focusing on the key mechanisms in the AH pathogenesis, effective blood pressure management and control can greatly reduce the risk of cardiovascular problems. This method highlights how important it is to have a thorough grasp of the functions and interactions of cytokines in the setting of arterial hypertension.

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