International Journal of Medical Sciences And Clinical Research
(ISSN – 2771-2265)
VOLUME 03 ISSUE 03 PAGES: 59-67
SJIF IMPACT FACTOR (2021: 5. 694) (2022: 5. 893) (2023: 6. 184)
OCLC – 1121105677
Crossref doi Google Scholar WorldCat MENDELEY
Publisher: Oscar Publishing Services

OSCAR PUBLISHING SERVICES

Journal Website: https://theusajournals.com/index.php/ijmscr

Research Article

THE ROLE OF CYTOKINES IN THE DEVELOPMENT OF ARTERIAL HYPERTENSION

Submission Date: March 21, 2023, **Accepted Date:** March 26, 2023,
Published Date: March 31, 2023
Crossref doi: https://doi.org/10.37547/ijmscr/Volume03Issue03-09

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ABSTRACT

Arterial hypertension (AH) is a common chronic disease characterized by a persistent increase in blood pressure. In addition to the main mechanisms of hypertension development, including activation of the sympathetic nervous system, disruption of the renin-angiotensin-aldosterone cascade, endothelial dysfunction, increased vascular reactivity, and vascular remodeling, it is assumed that inflammation is also involved in the formation of the disease. The review considers the involvement of cytokines in the pathogenesis of AH, as well as their interaction with blood pressure regulatory systems.

KEYWORDS

Arterial hypertension, inflammation, cytokines

INTRODUCTION

Cytokines are small protein molecules produced by activated immune cells. They play the role of mediators of intercellular communications in many normal and pathological processes of the body. The list of known cytokines is continuously growing, their receptors are being identified, the corresponding genes providing their synthesis, the data on the molecular basis of ligand-receptor interactions are being replenished. In addition, the number of pathological conditions in which cytokines are the subject of study is increasing. Their definition pursues various goals: involvement in pathogenesis, assessment of the severity of the course

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of the process, the effectiveness of therapy, etc. In recent years, the role of inflammatory mediators in the pathogenesis of arterial hypertension (AH) has been actively discussed.

Relevance. Arterial hypertension is one of the most common multifactorial diseases, affecting one third of the adult population in most countries of the world (28.5% in high-income countries and 31.5% in low- and middle-income countries) [1]. Of particular relevance to the study of hypertension is the fact that it is a risk factor for complications such as myocardial infarction, stroke, renal failure, vascular thrombosis, eye damage, etc. In addition, according to the World Health Organization, about 7.1 million deaths per year [2].

Essential arterial hypertension, or hypertension with unknown etiology, accounts for more than 90% of cases of hypertension [3]. It tends to be grouped in families and is a collection of syndromes with genetically based biochemical disorders [4,5]. Clinical phenotypes can be modified by various environmental factors, causing variation in blood pressure elevation and time of onset.

The pathogenesis of arterial hypertension is associated with genetic factors that contribute to the violation of the regulation of water-salt metabolism in the kidneys. The main mechanisms for the development of hypertension include activation of the sympathetic nervous system and disruption of the renin-angiotensin-aldosterone cascade. Endothelial dysfunction, increased vascular reactivity, and vascular remodeling are thought to be causes rather than consequences of increased blood pressure. In addition, isolated systolic hypertension in the elderly is associated with a decrease in vascular elasticity [3].

There is evidence of an association between hypertension and inflammation, but it is currently unclear whether inflammation is the cause of hypertension or its consequence.

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. Inflammation is a protective reaction of the body, usually arising from the introduction of infectious agents or injuries. This is a complex process that includes the activation of inflammatory cells and their migration to the affected tissues, elimination of the initiating agent, and repair of the injury site. During inflammation, there is an interaction between phagocytic cells of the innate immune system (APC - antigen presenting cells) and highly specific T cells of the adaptive immune system. Cytokines produced by APC, as well as other cells in the focus of inflammation, can affect the polarization of T cells and change their functions [6]. Molecules such as cytokines, nitric oxide, superoxide, and ligands for TLRs (Toll-like receptors) regulate the expression of vascular adhesion molecules and chemokines that facilitate T cell entry into target tissues. Often, in cardiovascular diseases, such nonspecific manifestations as an increase in C-reactive protein (CRP) or the presence of macrophages in tissues are associated with the inflammatory process [7]. CRP is an acute phase protein involved in innate immune responses and providing activation of the complement system and phagocytosis [8]. 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], 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. as an increase in C-reactive protein (CRP) or the presence of

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CRP is considered as an inflammatory marker associated with hypertension. This relationship has been confirmed by numerous clinical studies demonstrating an increased level of CRP in the blood plasma of hypertensive patients [10,11]. In addition, it was noted that patients with a tendency to increase blood pressure, as a rule, had a higher level of C-reactive protein in blood plasma than normotensive patients [12]. The role of cytokines in the development of arterial hypertension. Despite significant progress in understanding the role of inflammatory cytokines in the development of cardiovascular diseases [13], the significance of the quantitative expression of cytokines in the regulation of blood pressure and in the pathogenesis of arterial hypertension remains incompletely understood.

Harrison and colleagues [7] hypothesized that hypertonic stimuli promote the accumulation of activated T cells in perivascular adipose tissue and kidneys. In these places, activated T-lymphocytes secrete cytokines that affect neighboring vascular cells and the epithelium of the tubules of the kidneys. Consistent with this concept, subsequent studies have supported the hypothesis that cytokines produced by T-lymphocytes and other inflammatory cells contribute to hypertension. Studies have shown that the levels of cytokines IL-6 [14, 15], IL-1 [16], and TNF-α in blood plasma [17] of patients with arterial hypertension are higher compared to normotensive patients. The interaction of the pro-inflammatory cytokines IL-6 and TNF-α with blood pressure regulatory systems such as the renin-angiotensin and sympathetic nervous systems is known. The sympathetic nervous system stimulates the release of pro-inflammatory cytokines, and sympathetic nerves may be the source of their production [18]. In addition, there is experimental evidence for the activation of the sympathetic nervous system by pro-inflammatory cytokines [18]. Angiotensin II enhances the synthesis of TNF-α and IL-6 and activates the monocytic chemoattractant protein-1 and nuclear factor-kB [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]. Angiotensin II enhances the synthesis of TNF-α and IL-6 and activates the monocytic chemoattractant protein-1 and nuclear factor-kB [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]. Angiotensin II enhances the synthesis of TNF-α and IL-6 and activates the monocytic chemoattractant protein-1 and nuclear factor-kB [13, 19, 20]. Angiotensin II also increases the production of reactive oxygen

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species, including hydrogen peroxide, which are also involved in the inflammatory process [19, 20].

In addition, plasma levels of pro-inflammatory cytokines have been shown to correlate with an increase in blood pressure in experimental animals with AH [21]. For example, Alexander and colleagues [22] and LaMarca and his group [21] reported that doubling plasma levels of TNF-α increased blood pressure and renal vascular resistance in pregnant rats, and Orshal and Khalil [23] reported similar results when infused for 5 days with IL-6 in pregnant rats.

Li and colleagues [24] studied the role of endogenous IL-6 in the development of angiotensin II-induced AH. Male C57BL6 mice and IL-6 knockout mice were implanted with biotelemetry devices and placed in metabolic cages for continuous hemodynamic and metabolic control of chronic angiotensin-II-induced hypertension. Plasma levels of IL-6 were significantly higher in wild-type mice with chronic angiotensin-II hypertension. The main conclusion from this study is that hypertension caused by a chronic increase in angiotensin II is significantly dependent on the concentration of IL-6. IL-6 knockout mice had significantly lower mean arterial pressure (~30 mmHg) than wild-type mice during 2 weeks of angiotensin II infusion. These results clearly demonstrate the role of quantitative content of IL-6 in mediating chronic hypertensive response to angiotensin II. Moreover, the study showed that this was not post-angiotensin-II hypertension, and the difference in BP values between groups preceded urinary albumin excretion, suggesting that IL-6 contributes to angiotensin-II-induced hypertension through mechanisms independent of angiotensin II-induced kidney injury. Etanercept is a TNF-α antagonist that reduces fructose-induced BP [25], prevents vascular dysfunction and reduces angiotensin II-related hypertension, and lowers blood pressure in animals with chronic autoimmune inflammation [26]. In some cases, TNF-α antagonism prevents target organ damage without lowering blood pressure. For example, etanercept prevents kidney damage in saline-dependent hypertension without lowering blood pressure [27], and reduces albuminuria and renal inflammation in hypertensive transgenic rats [28]. Interleukin-6 is also involved in angiotensin II-induced but not salt-sensitive hypertension [29].

It has been established that the pro-inflammatory cytokine IL-17 contributes to the development of AH. This cytokine is produced by Th-17 cells, a subpopulation of CD4+ cells. IL-17 is involved in the pathogenesis of various diseases, including rheumatoid arthritis, inflammatory bowel disease, psoriasis, and inflammatory airway diseases [30]. IL-17 is also produced by CD8+ cells, neutrophils, and natural killer cells [7]. The increase in blood pressure in mice deficient in IL-17 was found to be similar to the increase in BP in wild-type mice, however, IL-17 -/- mice do not maintain hypertension. In addition, the increase in superoxide production and decrease in endothelium-dependent vasodilation observed in wild-type mice did not occur in IL-17-/- 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.In addition to Th-17 cells, there is another subpopulation of CD4+ cells that differs from the Th-1 and Th-2 subpopulations -

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regulatory T cells (Tregs). These cells are characterized by the expression of the transcription factor Forkhead (FoxP3) and the surface expression of CD25, and play a critical role in maintaining self-tolerance [32]. Genetic deletion of these cells by elimination of FoxP3 leads to severe fatal lymphoproliferative disorders [33]. Recent studies have shown that Tregs have a protective effect in hypertension. Kwaken et al. found that adoptive transfer of these cells does not affect the angiotensin II-dependent hypertensive response, but is involved in angiotensin II-induced cardiac injury. Tregadoptive transfer reduces cardiac inflammation, hypertrophy, and fibrosis caused by chronic angiotensin II-induced hypertension [34].

Wiel and colleagues studied rats carrying the Dahl salt sensitive (SS) genome on chromosome 2 of the Brown Norway rat strain (SSBN2) [35]. Chromosome 2 is known to contain genes associated with hypertension and inflammation and has loci for quantitative traits of hypertension. The authors found that SSBN2 rats have moderate hypertension, fewer inflammatory cells in the aorta, and less pronounced vascular hypertrophy than Dahl SS rats. They also showed that the aorta of these animals had more Treg cells, as evidenced by an increase in FoxP3b mRNA compared to Dahl SS animals. IL-10 is an important anti-inflammatory cytokine produced by Treg cells. Tregs of SSBN2 rats were found to produce more IL10 than Tregs of Dahl SS rats. The authors came to the conclusion that Tregs play an important role in reducing elevated blood pressure and target organ damage in SSBN2 animals. Consistent with the protective function of IL-10, Dieden et al found that incubation with angiotensin II resulted in carotid endothelial dysfunction in IL-10 –/– mice, but did so without damaging endothelium-dependent arterial vasodilation in normal mice [36]. These investigators further showed that angiotensin II increases vascular superoxide production in IL-10 –/mice, but not in wild-type animals. but does so without damaging endothelium-dependent arterial vasodilatation in normal mice [36]. These investigators further showed that angiotensin II increases vascular superoxide production in IL-10 –/mice, but not in wild-type animals. but does so without damaging endothelium-dependent arterial vasodilatation in normal mice [36]. These investigators further showed that angiotensin II increases vascular superoxide production in IL-10 –/mice, but not in wild-type animals.

Cytokines and endothelial dysfunction in arterial hypertension.Another mechanism by which inflammation may contribute to the development of hypertension is endothelial dysfunction. The endothelium is a layer of cells lining the inner surface of blood vessels involved in the regulation of vascular tone. Nitric oxide (NO), synthesized by endothelial nitric oxide synthase (eNOS), is a signaling molecule that plays an important role in the regulation of vasodilation. The release of NO from endothelial cells causes relaxation of vascular smooth muscles and their expansion [37]. Endothelial dysfunction can contribute to an increase in systemic vascular resistance and thus lead to the development of hypertension and usually manifests itself as a violation of endothelium-dependent vasodilation due to an imbalance between vasoconstrictors and vasodilators [38]. Inflammation, as previously found, suppresses the expression of NO-synthase. For example, CRP [39] and TNF [40] attenuate NO production by destabilizing eNOS mRNA, while TNF inhibition restores endothelial vasodilation in humans [41]. IL17 has been reported to cause endothelial dysfunction by activating Rho kinase, resulting in phosphorylation of the inhibitory residue of eNOS, threonine 495 [42].

It is important to note that normal endothelium has anti-inflammatory effects, such as NO-dependent

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inhibition of leukocyte adhesion [43]. Inhibition of eNOS activity enhances the expression of leukocyte adhesion molecules and chemokines, such as monocyte chemotaxis protein 1 (MCP-1) [44]. Thus, endothelial dysfunction associated with increased cytokine expression may further exacerbate vascular inflammation, which in turn may contribute to hypertension.

CONCLUSION

Thus, the study of markers of the inflammatory process in arterial hypertension contributes to the idea of their involvement in the pathogenesis of the disease. An increase in CRP, TNF-a, IL-1, IL-6 and their interaction with the regulatory systems of blood pressure - the sympathetic nervous and renin-angiotensin systems, endothelial dysfunction are associated with the inflammatory process in AH.

The involvement of cytokines in inflammation in hypertension has been confirmed in animal models and in humans. One of the hypotheses put forward suggests that inflammation and activation of the immune system are a response to a mild increase in blood pressure, which is usually considered benign. There is also such a clinical condition as "prehypertension", which probably initiates a more severe form of the disease.

Determining the immune mechanisms of the formation of arterial hypertension opens up new possibilities for the pathogenetic therapy of this disease. However, it should be taken into account that the biological effects of many cytokines have a high degree of identity, and focusing only on well-known cytokines may not reflect the true state of cytokine regulation. In addition, some cytokines are able to interact with the receptor components of the same receptor complexes. Effective reduction and control of blood pressure, achieved by regulating the central links in the pathogenesis of the disease, will contribute to the effective prevention of cardiovascular complications.

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