Inflammatory markers in patients with hypertension

Abstract

Hypertension is a chronic disease with high levels of morbidity and disability. Elevated blood pressure can lead to many complications and is the main risk factor for stroke, heart failure and nephropathy. Factors associated with hypertension and inflammatory response differ from those associated with vascular inflammation. The immune system plays a vital role in the pathophysiology of hypertension. Inflammation is particularly relevant in the progression of cardiovascular diseases, which has led to extensive research on inflammatory markers and indicators.

Key words: Hypertension; Immunity; Inflammation; Inflammatory marker

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Introduction

Essential hypertension is a common disease, the aetiology and pathophysiology of which result from the interaction of various systems. High blood pressure is a critical feature of several cardiovascular diseases, and the immune system and inflammatory response play a major role in the pathogenesis of hypertension. The increased levels of many inflammatory markers in patients with hypertension support the role of inflammation in the pathogenesis of hypertension (Pruijm et al, 2013). In individuals with normal blood pressure, the presence of these markers is associated with an increased risk of hypertension, while in patients with essential hypertension, the levels of these markers are related to target organ damage and can help predict the risk of cardiovascular events (Aydin et al, 2022). Therefore, understanding the role of inflammation in hypertension provides insights towards new treatment methods for hypertension and its complications. This article reviews clinical research on the relationship between inflammatory markers and indicators and hypertension.

Definition and pathogenesis of hypertension

Hypertension is a cardiovascular syndrome usually defined as systolic blood pressure ≥140 mmHg and diastolic blood pressure ≥90 mmHg. Blood pressure can be divided into four categories (normal blood pressure, normal–high blood pressure, grade 1 hypertension and grade 2 hypertension) and three levels of risk (low, medium and high). Hypertension-mediated organ damage is defined as structural or functional changes in the arterial vascular system and/or organs caused by elevated blood pressure (Unger et al, 2020). Hypertension occurs in 25–43% of the world's population over the age of 18 years (Huffman and Lloyd-Jones, 2017). It is the main modifiable risk factor for death from cardiovascular diseases. Hypertension may be secondary to various causes, but the majority of patients have primary hypertension with no secondary cause. Although treatment options have improved, 8–12% of patients with hypertension still have uncontrolled blood pressure despite being given treatment (Nguyen and Chow, 2021).

Short- and long-term blood pressure regulation involves the comprehensive action of multiple cardiovascular, renal, neural, endocrine and local tissue control systems. Activation of the innate immune system, inflammation and subsequent adaptive immune response leads to end-organ injury and dysfunction. Persistent low-grade inflammation in target organs may lead to impaired urinary sodium excretion, increased sympathetic activity and vascular endothelial dysfunction. This persistent low-grade inflammation may be an important factor causing the chronic increase in blood pressure in patients with essential hypertension (Caillon and Schiffrin, 2016; Rodriguez-Iturbe et al, 2017; Norlander et al, 2018).

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Inflammation and inflammatory markers

Inflammation is a complex process that occurs in response to biological, chemical or physical stimuli. It is a protective response to the presence of pathogens or foreign bodies, or an injury to the host tissue. This process is characterised by vasodilation, increased capillary permeability, increased blood flow and leukocyte recruitment. The loss of molecular mediators induced by inflammation is a signal to end the process and the subsequent response. The regression of inflammation and restoration of homeostasis are both passive and active processes, which are highly regulated and closely related to levels of inflammatory mediators.

Biomarkers have attracted increasing attention as indicators of disease status in patients with inflammatory diseases. As clinical research progresses, new indicators of disease activity have been found in peripheral blood and affected tissues through flow cytometry analysis of cell populations and detection of soluble media in serum (Tylutka et al, 2021). These emerging biomarkers can provide insights into the disease process, identify new therapeutic targets and provide short-term indicators of treatment success. Therefore, inflammatory biomarkers are powerful indicators of disease pathogenesis and severity, as well as response to treatment (O'Hara et al, 2006).

Proposed inflammatory markers include C-reactive protein, procalcitonin, erythrocyte sedimentation rate, serum amyloid A, interleukin (IL)-6, IL-8, IL-10, red blood cell distribution width, average platelet volume, neutrophil-to-lymphocyte ratio, lymphocyte-to-monocyte ratio and systemic immune-inflammation index (Bozduman et al, 2019; Al-Maiahy et al, 2021; Li et al, 2021; Xiang et al, 2021; Zhao et al, 2021). These markers have a variety of clinical applications in disease diagnosis and treatment, and have different expression pathways and pathophysiological mechanisms in cardiovascular diseases. One clinical example where the effect of inflammation is apparent in cardiovascular disease is in the rupture of atherosclerotic plaques. As plaque rupture is the basis of acute vascular events, levels of inflammatory markers are related to the development of atherosclerosis in patients with acute coronary syndrome (Dziedzic et al, 2022). Changes in haemodynamics, acute phase proteins, complement factors and cytokines are common in almost all inflammatory conditions and can be measured using a range of techniques.

Inflammation and hypertension

Although the exact pathophysiology of essential hypertension is not yet fully understood, endothelial dysfunction is considered to play a key role in the course of the disease. The vascular endothelium was initially thought to act as an inert barrier between the blood and blood vessels, but is now considered an important centre of vascular control. The endothelium plays an important role in regulating vascular wall tension, nutrient delivery, waste removal, inflammation, thrombosis and coagulation. Hence, hypertension is said to be, in part, an inflammatory disease (Gupta et al, 2011). Reactive oxygen species are produced by oxygen metabolism. Oxidative stress occurs when the level of pro-oxidative factors exceeds anti-oxidative factors, leading to the production of reactive oxygen species. Franco et al (2022) showed that oxidative stress plays an important role in the pathophysiology of hypertension.

Oxidative stress increases the production of proinflammatory factors, intensifying the inflammatory response (Tenório et al, 2019). A chronic and uncontrolled inflammatory state is caused by increased levels of pro-inflammatory immune cells and cytokines, and decreased levels of regulatory immune cells and cytokines (Harmon et al, 2016). Increased levels of tumour necrosis factor (TNF)-α and IL-6 in the vascular system can lead to endothelial dysfunction and progressive vascular endothelial injury, triggering extensive inflammation and cell damage (Winklewski et al, 2015). Hypertension is mediated by a variety of pro T-cell subsets (Ni et al, 2017). Activated T cells infiltrate the kidney and vascular system and produce cytokines, promoting renal sodium and water retention (Tylutka et al, 2022). In the vascular system, hypertension causes vasoconstriction and remodelling, leading to a marked rise in blood pressure (Zhang et al, 2021). Hypertension is related to the activation of the immune system, which leads to the recruitment and accumulation of immune cells

(especially lymphocytes and macrophages) in organs that control blood pressure (such as the vascular system and kidney). This immune infiltration promotes local inflammation and fibrosis, ultimately causing organ injury and poor control of blood pressure. Owing to the regulation of innate and adaptive immune responses, low-grade inflammation may be related to the occurrence and maintenance of hypertension.

Association of inflammatory markers with hypertension

Changes in levels of some serum inflammatory markers in patients with hypertension suggest that the inflammatory response plays an important role in the increase in blood pressure.

C-reactive protein

C-reactive protein, a typical acute-phase serum protein, is a marker of infection and its levels increase as a result of injury, systemic inflammation and other inflammatory stimuli. C-reactive protein is mainly synthesised in the liver in response to proinflammatory cytokines, especially IL-1, IL-6, IL-17 and TNF-α. C-reactive protein is also produced by mature adipocytes and leukocytes in response to lipopolysaccharides, and TNF-α production is stimulated by inflammation. C-reactive protein can enhance the production of chemoattractants and adhesion molecules in endothelial cells, including monocyte chemokine protein-1 and soluble intercellular adhesion molecule-1. High concentrations of C-reactive protein can predict adverse vascular events and directly inhibit nitric oxide production. This occurs partly through post-transcriptional effects on the stability of endothelial nitric oxide synthase mRNA, which reduces nitric oxide synthesis and promotes the development of various cardiovascular diseases (Verma et al, 2002).

C-reactive protein level is a sensitive and reliable marker of inflammation. Elevated levels of C-reactive protein impair endothelial regulation of vascular tone (Fichtlscherer et al, 2000). A prospective study showed that an increase in C-reactive protein levels positively correlated with the risk of hypertension (Sesso et al, 2003).

In individuals with hypertension, C-reactive protein levels are associated with vascular stiffness, atherosclerosis, end-organ damage and the development of cardiovascular events (He et al, 2022). Data in animal studies suggest that some antihypertensive drugs may reduce C-reactive protein levels in a manner unrelated to the effect on blood pressure. In people with normal baseline blood pressure, C-reactive protein levels have been shown to predict the occurrence of hypertension in multiple cohorts (Cheung et al, 2012; Kong et al, 2012; Chen et al, 2021). However, it is not clear whether the genetic variability affecting circulating levels of C-reactive protein is independent of environmental and behavioural factors. C-reactive protein is also considered a mediator of vascular remodelling in response to injury and cardiac remodelling in response to pressure overload.

Cytokines

Cytokines are a group of diverse, small proteins secreted by cells for intercellular signal transduction and communication. The main types of cytokines include interferon (IFN), TNF, IL, chemokines and colony-stimulating factors. Cytokines not only control cell proliferation and differentiation, but also regulate angiogenesis, immunity and inflammation. TNF-α is produced by various cells, including T cells, macrophages, endothelial cells and fibroblasts. It acts on two receptors – TNFR1 and TNRF2 – which are widely expressed. TNF-α negatively affects the production of endothelial nitric oxide, which may lead to hypertension through impairment of vasodilatation. In addition to its vascular effects, TNF-α also has renal effects that can affect blood pressure. Chronic exposure of renal parenchymal cells to TNF-α promote renal injury, shifting the urinary sodium excretion curve and increasing blood pressure. Banaszak et al (2019) found that children with hypertension had higher levels of TNF-α in their blood. Neuroinflammation is a common feature of renovascular, obesity-related and angiotensin II-mediated hypertension, and there is evidence that increased release of TNF-α contributes to the development of hypertension. Nonetheless, the underlying neural mechanism is unclear (Korim et al, 2019).

IFN-γ can promote hypertension by inducing the expression of angiotensinogen in hepatocytes and proximal renal tubular cells. Although angiotensinogen conversion is not considered the rate-limiting step in the systemic production of angiotensin II, its role in the tubular production of angiotensin II is more critical. The release of IFN-γ by killer T cells can regulate the production of local angiotensinogen, enhance sodium reabsorption and aggravate hypertension in a feedforward manner (Madej et al, 2018). Asadikaram et al (2019) showed that elevated serum IFN-γ levels might be involved in the pathogenesis of hypertension in patients with diabetes.

Interleukins are a diverse family of immune system regulators that play a role in the differentiation and activation of immune cells. The expression level of the plasma proinflammatory cytokine IL-12 has been shown to be higher in patients with hypertension than that in control groups (Ye et al, 2019).

Red blood cell distribution width

Red blood cell distribution width is an index used to measure changes in red blood cell size. This reflects the heterogeneity of red blood cell volume. It is traditionally used in laboratory haematology to distinguish and diagnose anaemia. An increase in red blood cell distribution width reflects a severe imbalance in erythrocyte homeostasis, which may be attributed to various metabolic abnormalities, such as oxidative stress, inflammation and malnutrition. Inflammation and oxidative stress can regulate the bone marrow response to erythropoietin by impairing iron metabolism and shortening erythrocyte life, thereby increasing the red blood cell distribution width. Some studies have shown that red blood cell distribution width can be used to predict the risk of cardiovascular disease (Buyukkaya et al, 2016; Seo et al, 2020).

The increase in red blood cell distribution width in patients with prehypertension and hypertension may reflect potential chronic inflammation. Higher red blood cell distribution widths are independently associated with an increased risk of death and cardiovascular events in patients with hypertension. Increased blood pressure is associated with increased red blood cell distribution width. Inflammatory cytokines and an increase in red blood cell distribution width can inhibit erythropoietin-induced red blood cell maturation by inhibiting the bone marrow.

Neutrophil-to-lymphocyte ratio

Neutrophil-to-lymphocyte ratio is a widely used inflammatory index that can be calculated during routine whole blood examinations. Neutrophil-to-lymphocyte ratio is an effective index to evaluate the prognosis of cardiovascular disease (Haybar et al, 2019). Azab et al (2010) found that neutrophil-to-lymphocyte ratio predicts adverse outcomes better than neutrophil or lymphocyte counts alone, because it considers two different parts of the immune system. Neutrophils play a role in active inflammation through the secretion of inflammatory mediators and oxygen free radicals, while lymphocytes are part of the regulatory pathways of the immune system (Azab et al, 2010; Afari and Bhat, 2016). Compared to many previously studied markers, neutrophil-to-lymphocyte ratio is a widely-used, cost-effective inflammatory marker (Templeton et al, 2014; Afari and Bhat, 2016).

A cross-sectional study showed that elevated neutrophil counts in the blood and neutrophil-to-lymphocyte ratios were closely associated with an increased risk of hypertension (Çimen et al, 2017). In addition to secreting catecholamine and acetylcholine, neutrophils also exhibit adrenergic regulation, which regulates vascular wall tension and causes elevated blood pressure (McCarthy et al, 2021). In patients with hypertension, the autonomic nervous system can activate neutrophils, which can cause vascular system damage, penetrate the arteries, heart and kidney, drive fibrosis by secreting oxidants and proinflammatory molecules, and promote the recruitment of other immune cells for tissue inflammation (Liu et al, 2015). Neutrophils regulate inflammatory processes and participate in the release of reactive oxygen species. Inflammation affects levels of nitric oxide, which can lead to vascular endothelial injury related to hypertension. In a large-scale epidemiological study in China, an elevated neutrophil-to-lymphocyte ratio was significantly associated with widespread hypertension (Liu et al, 2015).

Key points

- Hypertension is a chronic, low-grade inflammatory disease.
- Abnormal immune function is linked to a range of factors, from the occurrence and development of hypertension through to the damage of target organs.
- The mechanisms that trigger inflammation and immune activation in people with high blood pressure are not well understood.
- Better understanding of immune and inflammatory markers is expected to inform the development of new therapies for the treatment of hypertension and related cardiovascular diseases.

Mean platelet volume

Mean platelet volume is a quantitative measure of average platelet size and potential marker of platelet reactivity. Varol et al (2010) showed that higher mean platelet volume is associated with an increased incidence rate of hypertension, but is not related to other risk factors. This suggests that platelet activity may influence the incidence of hypertension (Varol et al, 2010; Gang et al, 2017). The chronic imbalance between endothelium-derived relaxing and contracting factors may lead to abnormal vasodilation and increased blood pressure (Bautista, 2003). Under physiological conditions, the vascular endothelium responds to mechanical and biochemical agonists by producing antiplatelets, anticoagulants, fibrinolysis, vasodilation and vasoconstrictors. Many cross-sectional studies have established a link between essential hypertension and the endothelium-dependent expansion of arterial circulation (Konukoglu and Uzun, 2017). Mean platelet volume is closely related to various cardiovascular diseases or risk factors (Bekler et al, 2015; Sansanayudh et al, 2016; Wan and Ma, 2017). Gokdemir et al (2019) showed that an increase in mean platelet volume is related to other markers of platelet activity, including increased platelet aggregation and thromboxane synthesis. The size and density of platelets vary between individuals, and mean platelet volume negatively correlates with platelet count and haematocrit. Larger platelets are more active in metabolism and enzyme catalysis and have higher homeostasis characteristics and greater thrombogenic potential (Chu et al, 2010).

There is evidence that mean platelet volume >12.5 fl is an independent risk factor for in-hospital mortality, particularly in patients with acute myocardial infarction (Liu et al, 2017). Karabacak et al (2014) found that a hypertensive crisis is an extreme phenotype of hypertension and hypertension-related thrombotic complications. Mean platelet volume increases in patients in the hypertensive emergency and hypertensive sub-emergency groups, and is independently related to systolic blood pressure. High mean platelet volumes are related to the balance of oxidative stress in vivo, resulting in high oxidative stress levels, which weakens the plasticity of red blood cells, and increases the adhesion between red blood cells and endothelial cells, promoting thrombosis.

Conclusions

Hypertension is a risk factor for cardiovascular disease, and inflammation and immune cells play an important role in the pathogenesis of hypertension. Moreover, hypertension is an inflammatory process involving immune cells, and an important component of end-organ damage associated with hypertension is mediated by inflammation. Elevated levels of serum inflammatory markers and indicators of inflammation have an early predictive effect on the occurrence of hypertension and relevant predictive value for its complications and prognosis. The specific mechanism of inflammation on hypertension remains to be further studied, and targeting these inflammatory markers may become the key to discovering new treatments for hypertension.

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Conflicts of interest

The authors declare that there are no conflicts of interest.

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