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PROINFLAMMATORY HUMORAL FACTORS AND THEIR ROLE IN THE PATHOGENESIS OF LEFT VENTRICULAR HYPERTROPHY IN HYPERTENSION (LITERATURE REVIEW)

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The aim of the research *was to consider the role of chronic low-grade systemic inflammation and a list of pro-inflammatory factors (interleukins, chemokines, tumor necrosis factor alpha, adipocytokines, metalloproteinases and their inhibitors, growth and inflammatory factors, etc.) as predictors of the onset and progression of left ventricular hypertrophy and myocardial fibrosis in individuals with hypertension*
Materials and Methods*: keywords search of native and foreign sources of literature from scientometric databases Google Scholar, Clarivate, Web of Science, Scopus, PubMed and its analysis, considering data from modern European and Ukrainian guidelines of recent years was performed.*
Results and Discussion. *Data on the conditional classification of pro-inflammatory and anti-inflammatory cytokines, their activity in hypertensive heart and diastolic dysfunction, a number of traditional pro-inflammatory factors from the superfamilies of interleukins, pentraxins and transforming growth factor beta 1 are considered, as well as new promising biomolecules that are used as indicators of chronic low-grade systemic inflammation, including the experiments on hypertensive animals. The question of the prospects of using a multi-indicator model of pro-inflammatory factors in individuals with arterial hypertension is considered, a brief description of promising targeted therapeutic approaches to inhibit pro-inflammatory mechanisms in patients with is given.*
Conclusions. *In the research works of the last 10 years, a high scientific interest in the pathogenetically significant role of chronic low-grade systemic inflammation, pro-inflammatory factors in the occurrence and progression of hypertensive heart disease and left ventricular hypertrophy has revealed, and the promise of using biomarkers as their indicators for further personalized treatment on this basis for this category of patients has proven*
Keywords: *arterial hypertension, chronic low-grade systemic inflammation, pro-inflammatory humoral factors, left ventricular hypertrophy, diastolic dysfunction, myocardial fibrosis, prediction of cardiovascular complications*

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1. Introduction

Arterial hypertension (AH) is one of the most widespread cardiovascular diseases (CVD) and, at the same time, the most significant risk factor (RF) for a number of cardiovascular complications, namely heart failure (HF), coronary heart disease (CHD), rhythm disorders, primarily atrial fibrillation (AF), cerebrovascular accidents, and chronic kidney disease (CKD). Diseases related to AH, primarily the components of the metabolic syndrome (MS) have already reached epidemic levels in developed countries, make a significant contribution to CV and the total mortality of the population of the world, Europe, and Ukraine [1].

A universal pathophysiological mechanism that causes the progression of the disease and worsens the prognosis of patients with AH should be considered hypertrophic remodeling of the left heart cavities, which is associated with the development of their fibrosis, the formation of signs of concentric hypertrophy of the left ventricle (LVH) and its diastolic dysfunction (LV DD) [2–4]. Due to its importance, this structural and functional reconstruction of the heart is defined in the modern English-language literature as "hypertensive heart disease" (HHD), and in Ukraine – as "hypertensive heart" (HH). Despite certain successes in inhibiting the progression of HH, the possibility of inhibiting myocardial fibrosis, LVH regression and restoring its diastolic function remains a significant problem [5–7]. Researchers currently believe that an important feature of all cardiovascular diseases, including arterial hypertension, is the activation of chronic low-grade systemic inflammation (CLGSI).

Research objective was to consider the role of chronic low-grade systemic inflammation and a list of pro-inflammatory factors (interleukins, chemokines, tumor necrosis factor alpha, adipocytokines, metalloproteinases and their inhibitors, growth and inflammatory factors, etc.) as predictors of the onset and progression of left ventricular hypertrophy and myocardial fibrosis in individuals with hypertension.

2. Materials and Methods

Keyword search of native and foreign sources of literature from scientometric databases Google Scholar, Clarivate, Web of Science, Scopus, PubMed and its analysis, considering data from modern European and Ukrainian guidelines of recent years was performed.

3. Results and Discussion

Left ventricular hypertrophy (LVH) in AH is associated with increased arterial stiffness, negative blood pressure (BP) patterns, and a number of humoral changes [2–4]. LVH with the AH is an independent RF for ventricular arrhythmias, sudden cardiac death (SCD) and significantly increases annual CV mortality [8].

From the **morpho-functional positions**, the formation of LVH is a gradually progressive multistage pathological process which is characterized by hypertrophy of cardiomyocytes (CMC), activation of their apoptosis, formation of interstitial and perivascular fibrosis, remodeling and rarefaction of coronary microvessels, violation of coronary hemodynamics, dilatation of the LV and left atrium (LA), development of LV DD, diastolic HF (DHF) and/or systolic HF with preserved ejection fraction (HFpEF) [9]. An important role in LVH as a trigger is attributed to microvascular dysfunction, increased stiffness of the CMC, endothelial dysfunction, chronic low-grade systemic inflammation (CLGSI) and myocardiofibrosis [10].

Among the **neurohumoral markers** of LVH, the activation of the renin-angiotensin-aldosterone and sympathetic nervous systems (RAAS, SNS) should be noted first of all. Activation of the production of angiotensin II (A II) initiates the formation of a significant number of powerful vasoconstrictor and pro-inflammatory biologically active molecules (pro-inflammatory and profibrogenic interleukins (IL), representatives of the TGF β1 family). This "scenario" occurs against the background of inhibiting the protective effects of anti-inflammatory cytokines, angio- and cardioprotective systems, primarily nitric oxide and vasodilating prostaglandins, causing shifts at the cellular level, contributing to the formation of the so-called "hypertensive myocardium" [11, 12]

Most authors consider the presence of CLGSI with the activation of a number of pro-inflammatory factors (IL, chemokines, TNF-α, adipocytokines, matrix metalloproteinases (MMP) and their inhibitors, growth factors, etc.), factors of oxidative stress (OS) and endothelial dysfunction to be an extremely important pathogenetic mechanism for the occurrence and progression of HH. CLGSI plays a key role in cardiac remodeling, and circulating pro-inflammatory factors are independently associated with the risk of development and negative course of AH and HF [13–15].

CLGSI in the **myocardium** leads to LVH, its DD, causes pathological remodeling of the LV, contributes to fibrosis, triggering a number of apoptotic factors [16–18]. A-II, the leading hormone RAAS, increases the production of reactive oxygen species (ROS) and pro-inflammatory cytokines (IL-1β, IL-6, TNF-α), while reducing the production of anti-inflammatory IL-10 and IL-35 [19, 20]. The presence of CLGSI is characterized by a decrease in the level of T regulatory cells, and an increase of IL 6, 17 and TGF β levels, and a decrease in the pool of IL 10 [21]. Dziedzic-Jankowska K. considers the ratio of monocytes to neutrophils as an immunological marker of LVH in children with primary AH [22]. Regarding the formation of LVH, a significant number of cells of the immune system in these conditions produce proinflammatory agents. First of all, these are monocytes, macrophages, T and B lymphocytes, adipocytes, vascular smooth muscle cells, CMC [23].

CLGSI in the **vessel walls** is associated with an increase in the production of ROS, a violation of the ratio of nitrate-nitrite anions (NO - NO_2-) with an increase in the latter (NO_2-), activation of OS, and changes in the fibrinolysis system [24]. In kidney, CLGSI in addition to cytokine "storm", is characterized by aldosterone release, microalbuminuria, interstitial fibrosis, Na retention, potentiating cardiac remodeling [25]. Such a well-known factor with pro-inflammatory properties as uric acid (UA) is associated with the presence of LVH, increases OS and promotes activation of the RAA system. A number of evidence-based reviews also support the role of hyperuricemia as a marker of cardiac remodeling and CV risk [26].

CLGSI in **adipocytic tissue** under the conditions of its infiltration by macrophages due to its activation by pro-inflammatory cytokines causes the progression of inflammation both in general and at the level of kidneys and epicardial fat, contributes to the release of adipocytokines, an excess of advanced glycation end products (AGE), increasing insulin resistance (IR), which is also associated with LVH.

This fact has already been confirmed both in the clinic and in an experiment on hypertensive animals. Treatment with mammalian target of rapamycin (mTOR) inhibitor everolimus ameliorated hypertension, left ventricular (LV) hypertrophy and fibrosis, and LV diastolic dysfunction, and attenuated cardiac oxidative stress and inflammation in metabolic syndrome (MetS) / obese rats [27].

Endothelial dysfunction, disturbances in the systems of OS, myocardial extracellular matrix (ECM), and glycation processes today are considered to be the triggers of CLGSI and remodeling of the myocardium.

Under conditions of CLGSI, the **endothelium** of coronary microvessels reduces the bioavailability of nitric oxide starts the cascade of OS factors, by increasing the production of ROS in conditions of imbalance in the system of pro- and anti-inflammatory cytokines, contributing to the development of LVH. Increased vascular permeability and stiffness, thrombus formation, and fibrosis, main effects associated with AH, are also initiated by inflammatory mechanisms. Endothelial dysfunction potentiates lipid metabolism disorders, adipose tissue hormone imbalance, contributes to the damage to the endothelium, which loses its anti-inflammatory, antioxidant, antithrombogenic properties, leads to impaired blood perfusion and the development of tissue hypoxia [16, 17]. In the implementation of the effects of CLGSI, the exogenous factors play an important role, primarily the Western diet, aging and reduced physical activity [18].

Markers of OS are closely related to the activation of low-intensity inflammation due to the excessive formation of TNF-α, IL-6 and ROS [14, 28]. The review by Boarescu PM and co-authors provides an overview of markers of OS, pro-inflammatory cytokines and histological changes in experimental AH, vascular disorders against the background of endothelial dysfunction and the formation of AGE [29].

ECM is also involved in cardiac remodeling in AH. ECM synthesis is promoted by pro-fibrogenic growth factors, primarily TGF-β1 [30]. Activation of representatives of this system of matrix metalloproteinases (MMPs) and their inhibitors occurs against the background of heart remodeling. MMP-2 is one of the main proteases secreted by CMCs, affects the function and structure of the myocardium by interacting with pro-inflammatory factors in AH. It was found that changes in MMP and their tissue inhibitor (TIMP) are significant indicators of asymptomatic LV DD [31]. Factors of the ECM are also associated with the expressiveness of LVH remodeling of the left heart cavities [30].

ROS are a co-product of normal oxygen metabolism, their excess leads to OS, plays a fundamental role in endothelial dysfunction [32]. The glycation process leads to the formation of glycosylation end products (AGEs). AGEs contribute to myocardiofibrosis, the formation of atherosclerotic plaque through the mechanism of non-enzymatic glycation of various molecules [33].

Proinflammatory factors which related to AH and associated with the presence of LVH belong to the **superfamilies of pentraxins** (C-reactive protein (CRP), pentraxin-3 (PTX3)), **IL and transforming growth factor β 1** (TGF β 1).

CRP, which belongs to the pentraxin superfamily, is one of the most important pro-inflammatory factors and at the same time an important indicator of CLGSI, a predictor of increased CV risk. In multicenter studies, it has been proven that the level of CRP or its highly sensitive form directly correlates with the presence of LVH, contributes to cardiac fibrosis. According to Song W, et al., high-sensitivity CRP (hs-CRP) is a potential predictor of LVH in elderly patients on AH. In this study, a cohort group of elderly individuals with AH demonstrated a strong association between hs-CRP levels and the presence of LVH. According to the authors' results, hs-CRP ≥ 1.25 mg/l can serve as an independent predictor of LVH in people with AH and demonstrate good diagnostic informativeness for LVH [34]. hs-CRP and circulating pro-inflammatory factors of pathological remodeling of the heart with AH and associated diseases were also reflected in the publications of scientists **of our department** [35, 36].

There is a sufficient evidence base for the role of CRP in hypertrophic remodeling under AH conditions. According to Cortez AF et al. [37], patients with CRP level above the median (3.8 mg/L, interquartile range: 2.0–7.2 mg/L) had a two-fold increased risk of serious CV events ($p = 0.002$) and an 86% higher risk of SCD ($p = 0.029$).

PTX3 together with CRP belongs to the above superfamily of proteins. PTX3 has five long monomers, their role relates to the interface of the immune system and the contractile function of the myocardium. The relationship between serum PTX3 levels and endothelial dysfunction has become an increasingly interesting scientific study due to the high potential of PTX3 as a prognostic factor for CV risk [38]. PTX3 was proposed as a new marker of LV DD depending on the BP profile. According to Mkhize SA and co-authors [39] circulating PTX-3 in an experiment on rats was positively associated with systolic BP, at the same time it had no probable relationship with LVH parameters. Thus, PTX-3 may be less involved in the development of LVH in SHR rats, but reflect the presence of chronic low-intensity inflammation that is associated with AH.

Among the factors associated with CLGSI under the conditions of AH, the **superfamily of cytokines** should be characterized. Depending on which cells of the immune system synthesize the cytokine, IL, lymphokines, myokines, adipocytokines, etc. are distinguished. In response to hypoxemia, CMCs and macrophages release pro-inflammatory cytokines, which have a cytotoxic effect on the myocardium, cause kidney damage, and stimulate the production of growth factors and fibrosis [40–42].

Numerous pro-inflammatory IL- IL-1α, IL-1β, IL-2, IL-6, IL-8, IL-11, 12, IL-17, 18, IL-23, 33, TNF-α, TGF-β and gamma interferon (IFN-γ) participate in the formation of LVH and LV DD under the conditions of HFpEF. An increase in the level of IL in this category of patients is directly related to the activation of A II, an increase in BP, the formation of LVH, and damage to target organs [43].

Among the pro-inflammatory cytokines, one of the key mediators of CLGSI is **IL-1**, which initiates an inflammatory reaction, participates in the pathogenesis of AH and LVH, promotes Na reabsorption, stimulates the formation of adhesion molecules [44].

IL-6 superfamily cytokines (IL-6, oncostatin M, cardiotrophin) and their pleiotropic effects play a key role in CLGSI, and cardiac remodeling. IL-6 plays an important role in the development of AH, hypertensive response to A II, cardiac fibrosis [45, 46]. According to Hasanah U et al., IL-6 is useful for detecting asymptomatic patients with components of MetS and LV DD, significantly increasing in them during the application of lifestyle correction measures [47].

A member of the IL-6 family, **oncostatin M** (OSM), produced by immune cells, has a wide influence on cell proliferation. High levels of OSM have been found in CLGSI and have been associated with myocardial fibrosis. Stawski L, Trojanowska M [48] discuss current views on the role of OSM in different stages of the fibrotic process. OSM, independently of IL-6, induced tissue fibrosis and cardiac dysfunction as emphasized by the authors of other studies [49].

González A et al [50] observed, that **cardiotrophin-1** (CT-1), which is a cytokine member of the IL-6 superfamily, produced by CMCs under biomechanical stress, leads to CMC hypertrophy and myocardial fibrosis. Recent data suggest that CT-1 can be used not only as an indicator of LVH and dysfunction in patients with AH, but as well as a potential target for therapy [51].

IL-8 increases the expression and production of osteopontin [52], which is associated with LVH, causes interstitial fibrosis, affects TGF-β, which stimulates col-

lagen synthesis and suppresses matrix degradation by reducing the activity of MMPs. IL-8 also plays a special role in the development and worsening of LV diastolic dysfunction [40]

IL-11 is pleiomorphic and targets cardiac myocyte effector pathways. One of the mechanisms by which IL-11 induces LV DD is myocardiofibrosis [53].

IL-12 and its family consists of IL-12, IL-23, IL-27 and IL-35. Hypertensive patients showed higher levels of the listed pro-inflammatory ILs and lower levels of anti-inflammatory IL-35 than control subjects. The levels of pro-inflammatory ILs were positively correlated with both SBP and DBP. According to Bhattarai U. et al. IL-12β blocking antibody significantly weakened the infiltration of LV immune cells, reducing its hypertrophy, fibrosis, and dysfunction in an **experiment on mice** [54].

IL-17 is a pro-inflammatory cytokine produced by cells of the immune system, mainly Th17 lymphocytes, associated with fibrotic phenomena. In patients with hypertensive myocardiofibrosis, there is an infiltration of CMCs with Th17-lymphocytes that express IL-17A. The data given in the review by Huang L. [55] indicate that IL-17A is involved in the BP regulation, in the occurrence and maintenance of AH, cardiac fibrosis, and the aggravation of nephrosclerosis.

IL-18 is a member of the IL-1 cytokine superfamily. An elevated level of IL-18 was detected in AH, atherosclerosis, CHD. An increase in the circulating level of IL-18 in patients with MetS components was established, its close correlation with the prediction of cardiovascular events and mortality from them among these individuals [56].

IL-33 modulates the processes of CLGSI by regulating the differentiation and functioning of T-helpers and macrophages. It affects cell growth, features of structural and functional remodeling of the LV of the heart, DD and is associated with concentric LVH [57]. The effects of IL-33 are mediated by peptide ST2 (Suppression of Tumorigenicity 2), which is a member of IL 1 receptors. Excess content of the soluble form of ST2 (sST2) leads to LVH, activation of fibrosis processes. The functional ligand of ST2 (ST2L) is IL-33, their binding stimulates mitogen-activated protein kinases (MAPK), which leads to the activation of nuclear factor κB (NF-κB), causing pro-inflammatory effects [57, 58].

Tumor necrosis factor alpha (TNFα) is one of the main mediators of inflammation and the most multifunctional pro-inflammatory cytokine. TNF-α is a useful tool for predicting the occurrence of LV DD, and its TNF-α receptors (STNFR1 and STNFR2) were the most activated in patients with AH with HFpEF LV DD [40]. TNFα is capable of inducing the process of apoptosis of immunocompetent cells, connective tissue cells, and CMCs through the activation of cellular caspases, initiating the development of CLGSI, influencing the heart remodeling, induced by OS, exerting a procoagulation effect, and causing renal and cardiac fibrosis in animals [59]. **IL-6 and TNFα** are also often used by researchers as indicators associated with LVH, cardiac remodeling under AH conditions, including as predictors of mortality.

Macrophage galectin-3 (Gal3) plays an important role in interstitial fibrosis [60], cell signaling, activity of inflammatory markers, which correlate with the presence of LVH under AH conditions [61].

Experimental studies on hypertensive animals have proven the pro-hypertrophic and pro-fibrotic role of a number of pro-inflammatory factors that require further study. A separate issue is the role of these factors in AH-associated diseases, primarily AF.

Thus, according to experimental studies, IL-1β suppresses the contractility of the myocardium in vitro in models of the isolated heart of hypertensive animals in CMC culture, induces their apoptosis, and impairs the function of the heart muscle. IL-1β affects potential-dependent calcium channels in CMCs of rat ventricles and inhibits the contractile function of the myocardium in an experiment [62]. **The effects of IL-1β as IL-18** are considered not only as pro-inflammatory factors, but also as secondary mediators of LVH in AH [63].

According to Matsushita N et al., IL-1β plays an important role in AF associated with AH and caused by BP overload in the experiment [64]. Tsioufis C. et al. conducted a study of markers for predicting AF in conditions of LVH. A heterogeneous group of molecular markers for AF includes furin, almost all considered pro-inflammatory factors (CRP, IL-6 and 11, IL-1β) and fibrosis (TGF β-1 and MMP) [65].

IL 2 is involved in the progression of fibrosis in the heart and lungs under conditions of HF, and administration of antibodies to IL 2 can stimulate the production of regulatory T cells, reduce ventricular hypertrophy and low-intensity inflammation in an experiment [66].

Studies have shown that the level of IL-17A is increased in animals with experimental AH, as well as in patients with mild or moderate AH. The differentiation of CD4+ T cells into Th 17 cells is facilitated by NaCl and IL-17, as it was demonstrated in an experiment that table salt directly changes several types of cells of the immune system, aggravates autoimmune inflammation, and causes AH [67]. Both IL-23 and IL-17 are elevated in several experimental rodent models of AH, as well as in humans on AH in observational studies. Recent preclinical studies have shown that administration of IL-23 or IL-17A causes an increase in BP with damage to target organs [68].

Dysfunction in the anti-inflammatory cytokine system is a significant factor in the progression of CLGSI, and cardiac remodeling under AH conditions. The group of anti-inflammatory cytokines that counteract cardiofibrosis and inhibit the effects of pro-inflammatory IL, together with IL-4, include IL-10, IL 22 and IL-35, which were reflected in relevant publications [40, 69]. For example, IL-22, a cytokine with anti-inflammatory properties belonging to the interleukin-10 family, discovered in 2000, significantly attenuates the manifestations of HF and inflammatory activity caused by BP overload [69].

Members of the TGF β superfamily play a key role in heart remodeling under AH conditions. The most studied and important is TGFβ -1, which regulates the state of the immune system and participates in CLGSI. The mechanism of its action is associated with the activation of intracellular proteins Smad 2/3 and mitogen-activating protein kinases (MAPKs) and the formation of a signaling complex – TGF-β/Smad 2/3, which is the

main inducer of the development of cardiofibrosis. Blocking specific TGF-β receptors inhibits the occurrence of LVH, disrupts the system of fibroblast-CMC interactions [70, 71].

Growth differentiation factor 11 (GDF11), an age-dependent factor, a representative of the TGF β family [72]. GDF 11 is a protein with cardioprotective and antifibrogenic properties, which inhibits adipocytogenesis, participates in the processes of CLGSI in the myocardium. Current data on myocardial fibrosis indicate that GDF11 can also act as a pro-inflammatory agent [72–74].

Growth differentiation factor 15 (GDF-15), belongs to the TGF β superfamily, plays an important role in the regulation of the inflammatory response, and predicts CV events in the general population. An elevated level of GDF-15 was found in patients with AH, HF, AF, and CKD. GDF-15 is also an indicator of hemodynamic load, apoptosis and remodeling of the heart muscle. GDF-15 plays a protective role by inhibiting apoptosis, hypertrophy, and adverse remodeling via the PI3K-Akt, ERK1/2, and SMAD 2/3 pathways. GDF-15 also has the ability to screen for the risk of developing LV DD in healthy individuals and increase the accuracy of diagnosis of asymptomatic LV DD [75].

Chemokines are a group of low molecular weight pro-inflammatory cytokines with a wide range of immunoregulatory functions. According to Rudemiller NP [76], the expression of chemokines in tissues is increased in clinical and experimental AH. CCL2 and CCL5 chemokines have specific effects on BP and cardiac tissue damage. Chemokines of the CXC family contribute to an increase in BP, LVH and damage to target organs [77].

Adipocytokines (adipokines) are polypeptide hormones that contribute to obesity-related CLGSI. In a review by Hogas S, [78] the role of adipocyte markers of vascular inflammation, endothelial dysfunction, and cardiofibrosis in the pathogenesis and prognosis of CV pathology is described. Adiponectin (APN) has an anti-inflammatory and antihypertrophic effect, and hypoadiponectinemia caused by AH increases LVH, DD and causes diastolic HF. Peer M [79] considers APN as an independent factor in the occurrence of LVH with AH without the presence of diabetes.

Myokines – peptides that are formed in the body in response to muscle contraction, regulate the activity of adipose tissue. Recently described myokines are adropin and irisin [80]. In experimental studies, irisin reduced BP via NO-dependent pathways, played a role in vascular calcification and LVH formation [81]

Single works have provided data that such biomolecules as **thrombospondins** (TSP), which are regulators of the activity of MMPs, play a role in the development of cardiac remodeling and LVH. Thus, TSP – 4 takes part in heart remodeling induced by A II in the experiment [82], **cyclophilin A** (CyPA) promotes hypertrophy of CMC, causes dysfunction of ECM by activating MMP. A review by Cao M et al [83] aims to review the role and mechanism of action of CyPA in cardiac hypertrophy and remodeling. **Sirtuin 1** (SIRT1), as stated by Duman H and co-authors [84], which has anti-inflammatory, antioxidant and anti-apoptotic effects, is directly related to LVH, endothelial dysfunction, the presence of which is associated with general aging of the body.

Among other pro-inflammatory factors that may be associated with the presence of LVH and diastolic dysfunction under AH conditions, some biomolecules can be mentioned. Thus, **monocyte chemoattractant protein 1** (MCP-1), which induces the release of TGF-β and the development of reactive fibrosis, participates in cardiac remodeling and the progression of LV DD. The level of MCP-1 was also increased along with IL-6 and 8 in patients with AH with LV DD [85]. **Connective tissue growth factor** (CTGF) is a new marker of tissue fibrosis, along with TGF-β1. According to the data obtained by Chi H and co-authors [86], the levels of CTGF and TGF-β1 in plasma increased significantly, correlating with the severity of DD in patients with diastolic HF.

Cardiac myosin-binding protein-C (cMyBP-C) is a component of the cardiac sarcomere and regulates cardiac contraction and relaxation. Zhou X. et al. [87] demonstrated that increased S-glutathione of cMyBP-C correlates with LV dysfunction in humans and animal models. **Macrophage migration inhibitory factor** (MIF) is an immunoregulatory pro-inflammatory cytokine, has a chemokine-like effect, is involved in the stress response, lipid metabolism disorders, and endothelial dysfunction. In AH, in an experiment, MIF inhibits autophagy of CMCs in order to preserve normal heart geometry and protect against hypertrophic reactions, and its deficiency increases the progression of LVH [88].

Now many researchers consider the issue of the combined determination of a number of pro-inflammatory factors in a multi-indicator model for LVH under AH conditions (sST2, MMP-3, CT-1, adipokines and galectin-3) [61, 78].

Thus, in patients with primary AH, the levels of hs-CRP, TNF-α, IL-17A, and IFN-γ were correlated with the parameters and function of the left ventricle (LV), which indicates that inflammatory cytokines may be involved in the process of abnormal structure and function of the LV under conditions of primary AH. In addition, hs-CRP can be used as a health screening indicator for patients at high risk of LVH, according to Zan Y [45].

According to Wang X [61], probably higher levels of sST2, MMP-3 and Gal-3 in blood serum were observed in patients with AH with LVH. A review by Hogas S [78] describes the role of individual markers of vascular inflammation, endothelial dysfunction, cardiovascular fibrosis, and finally discusses the potential use of CT-1, leptin (a helical cytokine similar in structure to IL 6), adiponectin, resistin, and galectin-3 as indicators for various cardiovascular conditions, including LVH.

Considering the factors presented in the review, the targets for pathogenetically based therapy of HH are the blocking of aldosterone-activated mineralocorticoid receptors (MCR) and the reduction of RAAS A-II hormone release, which induce mitochondrial dysfunction and deterioration of myocardial relaxation. Traditional cardiovascular drugs (ACE inhibitors / AII Receptor Blockers ARBs, calcium channel blockers, MCR antagonists MCRA, statins) have already demonstrated additional pleiotropic anti-inflammatory effects, the ability to inhibit low-intensity inflammation, myocardial fibrosis, and reduce LVH [89–91]. It arouses interest and questions about the role of gene polymorphisms and the activity of proinflammatory IL receptors, their functions in LVH and DD,

and the prospects of the therapeutic potential of IL receptor blockers and monoclonal antibodies against inflammatory indicators in AH with HH, atherosclerosis, and HF [59, 92, 93].

The problem of hypertension with signs of hypertensive heart currently is in the legalization and wider use the term "hypertensive heart disease" now, its consideration as a therapeutic target for LVH regression, according to the researcher's majority [5–7]. Under conditions of hypertension, an important place in the LVH formation the chronic low – grade systemic inflammation and immune mechanisms is given, which not only go hand by hand with haemodynamic and neurohumoral factors, but also possibly precede them, state the scientists [13–18].

Thus, the determination of circulating humoral factors of inflammation is a modern informative approach to the diagnosis and prediction of the development of heart lesions in AH. First of all, such as HH, namely hypertrophy of the LV, myocardial fibrosis, diastolic dysfunction of the LV and HF with a preserved ejection fraction, both in the clinic and in experiments on hypertensive animals, regarding further personalized treatment on this basis of such category of patients. The most practical significance is the introduction into clinical practice of only carefully studied biological indicators (hs-CRP, IL-1,6, 18, 33, TNF-α, representatives of the TGF β1 family) [68–72], which have already convincingly demonstrated their diagnostic and prognostic value in clinical studies. Data obtained on animal models regarding the role of such biomolecules as IL-1β,2, 17A, 23, MIF in hypertrophic remodeling and fibrosis in AH require further study.

The implementation of targeted immunomodulatory therapy, primarily interleukin receptor blockers and monoclonal antibodies [59, 92, 93], which inhibits pro-inflammatory factors, reducing chronic low-grade systemic inflammation and activation of neurohumoral systems has undoubted prospects in preventing the progression of left ventricle hypertrophy, myocardiofibrosis, improving the diastolic function of the left ventricle before the appearance of heart failure, even with a preserved fraction emission.

Study limitations. The limitations of the study are related to the need to select and further analyze a narrower group of individuals with hypertension, namely with signs of LVH and activation of pro-inflammatory factors, insufficient financial support for access to some full-text versions of articles, and a certain lack of time to perform the work.

Prospects for further research. Within the framework of the department's research work, further study of the role of pro-inflammatory markers, such as hs - CRP and IL-6, in diseases associated with arterial hypertension (type 2 diabetes, atrial fibrillation), CVD risk factors that are modified with both clinical and subclinical target organ damage in individuals exposed to chronic wartime stress with different CVD risk profiles is planned.

4. Conclusions

In the research works of the last 10 years, a high scientific interest in the pathogenetically significant role of chronic low-grade systemic inflammation, pro-inflammatory factors in the occurrence and progression of hypertensive heart disease and left ventricular hypertrophy has revealed, and the promise of using biomarkers as their indicators for further personalized treatment on this basis for this category of patients has proven.

Conflicts of interest

The authors declare that they have no conflict of interest in relation to this research, whether financial, personal, authorship or otherwise, that could affect the research and its results presented in this article.

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Data availability

Manuscript has no associated data.

Use of artificial intelligence

The authors confirm that they did not use artificial intelligence technologies in creating the submitted work.

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Authors' contributions

Myloslavskyi Dmytro: Writing – Original Draft Preparation, Writing – Review & Editing; Koval Sergiy: Conceptualization, Supervision; **Mysnychenko Olga:** Resources, Data Curation; **Lytvynova Olga:** Supervision, Project Administration; Shcheniavska Olena: Resources, Writing – Review & Editing.

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