Morphometric and morphological changes in the spleen in the context of experimental modeling of chronic kidney failure

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Abstract: The article explores the structural alterations in the spleen resulting from chronic kidney failure using experimental animal models. Through detailed histological and morphometric analyses, the study reveals significant changes in spleen architecture, including lymphoid depletion, vascular alterations, and disruption of the white-to-red pulp ratio, which correlate with the progression of CKF. These findings suggest that chronic renal dysfunction exerts a systemic impact extending to lymphoid organs, underscoring the spleen's potential role in the immunopathogenesis associated with CKF and highlighting its value as a secondary indicator in experimental nephrology.

Keywords: chronic kidney failure, spleen morphology, morphometric analysis, experimental nephrology, lymphoid tissue, systemic pathology

In recent years, an increase in kidney disease has been observed. Currently, the main nosologies leading to chronic kidney failure include diabetes mellitus, arterial hypertension, chronic glomerulonephritis, as well as combinations of these diseases [4,18,25].

It is known that the prevalence of chronic kidney diseases and kidney failure varies across different regions and remains a serious and pressing issue in the field of healthcare. According to statistical data, in 2017, 1.2 million people worldwide died from chronic kidney failure. From 1990 to 2017, the global mortality rate from chronic kidney failure among individuals of all ages increased by 41.5%, although there were no significant changes in the age-standardized mortality rate. The global prevalence of chronic kidney failure among all age groups increased by 29.3% during this period [6,14,31].

It is worth noting that the clinical manifestation of chronic kidney failure develops with the loss of 70-75% of functional nephrons. As the condition worsens, the number of nephrons decreases further. The causes of this pathology are highly diverse: they include congenital anomalies (such as polycystic kidney disease, hydronephrosis, renal hypoplasia) and acquired, undiagnosed inflammatory diseases (such as pyelonephritis and glomerulonephritis), nephropathies caused by medications (e.g., aminoglycosides, cytostatic drugs), or the consequences of

infections, metabolic disorders (such as diabetes mellitus), autoimmune diseases, and more [1,10,26,28].

Despite the kidneys' high compensatory capacity (even the remaining 10% of nephrons can maintain water-electrolyte balance in the body), in the early stages of chronic kidney failure, quantitative disturbances in blood electrolytes, acidosis, impaired protein metabolism, and the retention of metabolic products such as urea, creatinine, and uric acid are observed, with their levels increasing. To date, more than 200 substances with disrupted metabolism during kidney failure have been identified [12,13,22].

Pathological changes in kidney function lead to a disruption of the body's internal environment stability (homeostasis). With a decline in glomerular filtration rate and the progression of uremia, metabolism slows down, altering the transport and binding processes of many biologically active substances, including pituitary hormones, to target cells. Thus, chronic kidney failure (CKF) leads to an increase in the levels of prolactin, luteinizing hormone (LH), and follicle-stimulating hormone (FSH). In this patient group, the levels of growth hormone (GH), insulin-like growth factor-1 (IGF-1), thyroid-stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), and vasopressin may remain within normal values or increase.

Hemodialysis does not reduce the levels of prolactin, LH, and FSH; however, it normalizes the concentrations of growth hormone, IGF-1, and TSH. The levels of ACTH and vasopressin may remain unchanged or decrease [5,9,18].

According to D.B.Avezova, three morphological stages of acute lung injury in chronic kidney failure can be distinguished. The first stage is the early exudative phase (up to five days), characterized by capillary congestion, alveolar collapse, microthrombosis, alveolar damage, neutrophil infiltration, pulmonary edema, and the presence of hyaline membranes and fibrin in the alveoli.

The second stage is the fibrinoproliferative phase (from six to ten days). During this stage, pulmonary edema gradually resolves, and fibroblast proliferation begins.

The third stage, starting from the tenth day after the onset of acute lung injury, involves fibrous destruction, characterized by the appearance of connective tissue (cells and fibers) in the areas of damage.

In all stages, the primary decompensating factor is the development of pulmonary edema, which is facilitated by increased permeability of the components of the air-blood barrier. The emergence of acute emphysema is a compensatory mechanism. Atelectasis and distelactasis occur when bronchioles are blocked by secretions, desquamation, and epithelial cells, and when type II alveolocytes, responsible for the synthesis and secretion of surfactants, are damaged. This leads to further progression of structural changes in the lungs and exacerbation of hypoxia [2,15,20,23,27].

The risk factors for the development of chronic kidney failure largely overlap with those for cardiovascular disease, with the most significant being arterial hypertension and metabolic disorders such as hyperglycemia, dyslipidemia, hyperuricemia, and obesity. Additionally, kidney damage caused by the toxic effects of medications (analgesics, NSAIDs, nephrotoxic antibiotics, and radiographic contrast agents) and smoking also play a crucial role [38].

The early signs of chronic kidney failure include microalbuminuria (MAU) and a decrease in glomerular filtration rate (GFR), which is recommended to be calculated using the MDRD formula (6). The resulting value is used to differentiate the stages of the disease and as a prognostic factor. MAU, proteinuria, and a decline in GFR to <60 ml/min are also independent risk factors for the development of cardiovascular disease. Therefore, patients with kidney pathology fall into the group of maximum cardiovascular risk.

The central link in cardiorenal interactions is the renin-angiotensin-aldosterone system (RAAS), endothelial-dependent factors, and their antagonists-natriuretic peptides and the kallikrein-kinin system. Activation of the renin-angiotensin and sympathetic nervous systems, the development of endothelial dysfunction, and chronic systemic inflammation lead to damage in one organ triggering damage in another, ultimately resulting in the development of cardiorenal syndrome (CRS) [19].

Changes in the skeletal system are among the severe complications of chronic uremia. Over the past decade, a steady increase in the number of patients with chronic kidney failure (CKF) worldwide has been observed, along with a trend toward increased life expectancy due to kidney replacement therapy. Involutional anatomical and functional disorders, which directly affect the kidneys, begin at around forty years of age. Among the many metabolic consequences of kidney failure, electrolyte imbalance syndrome is one of the most significant and develops in almost 100% of cases in patients undergoing hemodialysis [35,37].

Adequate program-based hemodialysis, which partially mitigates many metabolic disorders, generally does not positively affect phosphorus-calcium metabolism. Currently, it is not possible to differentiate changes in bone tissue in CKF solely through biochemical tests, though these tests are used to monitor treatment effectiveness. Thus, to observe the progression of functional disorders into gross morphological changes in organs and tissues, regular monitoring of blood calcium, phosphorus, alkaline phosphatase, parathyroid hormone (PTH), as well as vitamin D and aluminum concentrations, is conducted [11,22,32].

In recent decades, new clinical and experimental data have been obtained that deepen our understanding of the immune system’s state and the possible pathways of immunopathogenesis in chronic kidney failure. It is known that a characteristic and consistent change in the immunogram for the active phase of the disease is a

significant decrease in immunoglobulin levels in the blood, particularly IgG. This is primarily due to impaired synthesis and, to a lesser extent, protein loss in the urine. A decrease in IgA concentration is less frequently observed, while IgM and IgE levels are often elevated. The reduction in IgG production by B cells and the increased synthesis of IgM and IgE by B cells have been found to result from disrupted T-cell regulation, particularly a defect in the switching of IgMB cell activity [40].

According to Zueva T.V. and colleagues, acute coronary syndrome, stroke, hemorrhagic complications, acute heart failure, and high rates of atrial and ventricular fibrillation are associated with impaired kidney function [15].

In patients with chronic kidney failure, the response of lymphocytes to polyclonal activators is diminished. When the patient's cells are incubated not with autologous serum but with normal human serum, this response is partially restored. This suggests both a defect in the lymphocytes and the presence of inhibitors in the serum that cause "immunological autosuppression." The phenomenon of inhibition of lymphocyte blastogenesis in healthy individuals in vitro has been observed upon the addition of plasma from patients with kidney disease, further indicating the presence of an active circulating immunosuppressive factor in these patients [29].

One of the factors contributing to the generalization of inflammation in chronic kidney diseases is the activation of cytokine production and secretion, leading to increased cytokine levels in the blood. At the same time, activated monocytes and tissue macrophages synthesize both pro-inflammatory and anti-inflammatory cytokines. These cytokines attract effector cells (neutrophils and macrophages) to the site of inflammation, enhancing their phagocytic and bactericidal activities and initiating antigen-specific immune responses. It should be noted that the protective role of anti-inflammatory cytokines manifests when these mediators act locally at the site of inflammation. However, excessive and systemic production of anti-inflammatory cytokines leads to the development of organ dysfunction [17,36].

In chronic kidney failure, the level of vascular endothelial growth factor is a risk factor for reduced glomerular filtration rate and the development of vascular stiffness. An increase in C-reactive protein levels is associated with increased vascular wall stiffness, and the concentration of vascular endothelial growth factor is related to hyperfibrinogenemia. It is apparent that the increase in arterial stiffness in chronic kidney failure contributes to the rapid development of systemic atherosclerosis [3,21].

In their research, Emanuel V.L. and his students studied the value of annexin-5 as a biochemical marker for the preclinical stage of atherosclerosis in patients with chronic kidney failure who showed no clinical signs of atherosclerosis. The authors demonstrated that a decrease in glomerular filtration rate is accompanied by an

increase in annexin-5 levels, and its concentration is correlated with the indicators of the blood lipid spectrum [30].

Although the specific molecular mechanisms causing pathological damage to the renal system are still being studied, research shows that obesity is associated with chronic low-grade systemic inflammation due to the reduced levels of several anti-inflammatory cytokines produced by the spleen, such as tumor necrosis factor (TNF)-alpha and IL-6 [34]. Furthermore, IL-10 levels are reduced in obesity, possibly due to a decrease in CD20 expression on B cells that produce IL-10. A fatty diet leads to various morphological changes in the kidneys, including glomerular hypertrophy, a decrease in nephrin levels, and an increase in desmin levels, which are compensated by anti-inflammatory cytokines such as IL-10 produced by the spleen. Thus, the disruption of splenorenal interactions in obesity may contribute to the development of chronic kidney failure in patients with these risk factors [32].

The results of the conducted study indicate that under the influence of two different factors, the activity of Na^+-K^+-ATPase, Ca^{2+}-ATPase, Mg^{2+}-ATPase, and Ca^{2+}-Mg^{2+}-ATPase in spleen tissues significantly decreased within certain time limits compared to the control group. ATPases are membrane-associated proteins found in all cells, and their function is to maintain chemical and electrical gradients across the cell membrane. The energy that sustains this electrochemical gradient comes from the hydrolysis of ATP to ADP [33].

The energy maintained in this gradient regulates membrane transport, cotransport, and other metabolic systems of substances; ensures the movement of cations, anions, amino acids, and glucose across the cell membrane; and maintains the vital functions of the cell, including membrane electrical potential, cell volume, and the intracellular concentrations of Na+, K+, and Ca²+. The degree of cell damage is closely related to ATPase activity. Any substance or clinical condition that alters the normal cytomembrane ATPase activity inhibits ion transport between the internal and external parts of the cell, changes the electrochemical gradient, and leads to a broad range of cellular dysfunctions, resulting in the deterioration of organs and morphological damage. The presented data also suggest that inhibiting membrane pump activity is part of the pathogenesis of spleen damage in the development of chronic kidney failure. In addition to the direct damage caused by toxic substances, serious disturbances in the internal environment, such as the imbalance of fluids and electrolytes, accumulation of metabolic waste products, and disruption of energy metabolism, may be responsible for this pathogenesis [39].

The spleen consists of two types of tissue: white pulp and red pulp. The white pulp contains lymphoid cells and white fibers that play a role in the body’s immune defense. The red pulp consists of red blood cells, white blood cells, and platelets, which participate in blood formation and breakdown. The spleen has a rich network

of blood vessels, which is an integral part of its structure, ensuring a constant blood supply [7,8]. These vessels also serve to remove damaged or old cells from the blood. Overall, the spleen performs important functions in immunity and hematopoiesis, making it a vital organ for maintaining health and well-being. Kidney failure can affect the spleen, as the kidneys and spleen are closely interconnected. Kidney failure can lead to changes in blood levels of iron, calcium, and other substances, which can impact the function of the spleen [31].

Currently, the primary goal of specialists is to correct the pathogenic mechanisms of chronic kidney failure through various methods, slow the progression of the disease, improve the quality of life of patients, and extend their lifespan and the period before dialysis. This remains one of the pressing issues. Around the world, several scientific studies are being conducted on compensating glomerular microcirculation by coordinating the homeostasis system in patients with chronic kidney disease and implementing the functional reserve gradient of the kidneys.

A review of existing literature revealed that there is a lack of information regarding the effects of structural and morphological changes in the structure of chronic kidney failure, and much of the available data is outdated.

Conclusion. Modern science not only aims to identify and explain the phenomena of development but also allows for the management of biological processes through mechanisms that regulate them. Therefore, the study of tissue and organ relationships through morphology is a relevant and promising field. In chronic kidney failure, the level of vascular endothelial growth factor is also dangerous due to the reduction in glomerular filtration rate and the emergence of vascular stiffness. Thus, chronic kidney failure leads not only to dysfunction in all the body’s organs and systems but also causes morphological changes in the spleen, making it a disease of medical and social significance.

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