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Structural and Functional Changes and Endothelial Dysfunction of Blood Vessels in Chronic Kidney Disease

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Abstract

This review article discusses a number of factors affecting structural and functional changes, morphological alterations, and vascular permeability in chronic kidney disease. It also reflects views and opinions on the analysis of studies conducted in subsequent decades on the pathological profile of endothelial dysfunction indicators. At the same time, various areas for future research in this field are discussed.

Keywords: Chronic kidney disease, vessels, nitric oxide, endothelium, dysfunction.

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1. Introduction

Chronic kidney disease (CKD) is currently a global problem in modern medicine. A large portion of the world's population, approximately 13%, suffers from this disease, and this number is increasing by 5-8% annually [9]. Due to the disease's long latent period, the majority of patients with kidney disease are unaware of their impaired renal function, which remains the primary reason for the progressive increase in the disease's incidence. For example, in the United States, only one in ten of the 37 million people with CKD is aware that they have the condition [9, 12]. If the approach to CKD diagnosis has reached this state in a developed country, it is not difficult to imagine how much more severe the problem has become in developing and other socio-economically disadvantaged nations.

Preventing and slowing the progression of endothelial dysfunction in chronic kidney disease (CKD) is a priority in modern clinical nephrology. The fact that CKD is a risk factor for cardiovascular diseases (CVD) — and conversely, that there are numerous irrefutable factors in CVD pathologies that cause the progression of renal failure — provides the basis for systematic monitoring of vascular health. Furthermore, the increasing age of CKD patients and, conversely, the decreasing age of patients with cardiovascular diseases in recent years underscore the necessity of strengthening our approach to this problem [1,

2, 7]. It is well-known that the absolute number and proportion of elderly (60–74 years) and old (75–90 years) people are increasing worldwide, particularly in developed countries. According to forecasts by demographers and sociologists, this population aging will continue, and by 2025, the number of people aged 60 and older will increase fivefold [11]. With age, arteriolo- and nephrosclerosis develop, and the elasticity of the renal arteries decreases, which leads to an average annual decline in function of 1% after the age of 50 [11]. In older age groups, a decrease in baroreceptor sensitivity, sodium retention, and reduced elastin levels negatively affect the morphofunctional state of the blood vessels. The endothelium is one of the most critical criteria that determines this morphofunctional landscape of the blood vessels.

Since the late last century, the structural and functional state of the cells lining the interior of blood vessels has been actively studied. Currently, the endothelium is considered the largest endocrine organ [16]. The mass of the endothelium, which consists of one trillion cells, is approximately 1,500–1,800 grams [4].

According to I.Yu. Panina et al., the total length of the endothelial monolayer is 7 km, and its surface area is equivalent to that of a large football field [8]. The endothelium, as an autocrine and paracrine organ, is expressed in all organs and tissues [16]. It should be noted that the morphological structure of the endothelial layer of internal organs is not uniform. The heterogeneity of the endothelium depends on the organ's structure, biochemical composition, and function [14, 15]. For instance, the endothelium of pulmonary, renal, cerebral, or coronary blood vessels differs significantly in terms of genetic and biochemical specificity, receptor types, and protein composition—namely, the precursors of enzymes and transmitters. Consequently, pathophysiological changes develop selectively in individual vascular and capillary cells. The endothelium of various organs and tissues in the body is not equally susceptible to atherosclerosis, ischemic diseases, and edema development [8]. The endothelium produces substances that participate in maintaining vascular tone, blood pressure, the coagulative properties of blood, myocardial contractile activity, and brain metabolism, as well as in regulating the filtration capacity of the kidneys [8]. According to the literature, the endothelium controls the diffusion of water, ions, and metabolic products and responds to the mechanical effects of intravascular fluid with compensatory adaptation. Furthermore, the endothelium is sensitive to chemical and structural damage, which can enhance the aggregation and adhesion of formed elements, leading to the development of thrombosis and the deposition of lipid particles on the vascular surface. Under physiological conditions, in response to these stimuli, the endothelium increases the synthesis of nitric oxide (NO), endothelium-derived hyperpolarizing factor, and prostacyclin.

It has been noted that endothelial function can be defined as a balance of counteracting factors: relaxing and vasoconstrictor, anticoagulant and procoagulant, and proliferative and antiproliferative factors [8]. There are suggestions that NO suppresses the proliferative reaction of smooth muscle cells of the vascular wall and inhibits the aggregation of platelets, low-density lipoproteins (LDL), and the expression of adhesion molecules. Furthermore, NO prevents the adhesion of monocytes and platelets to the vascular wall and reduces endothelin secretion. Currently, well-studied endothelial vasoconstrictors include angiotensin II, thromboxane A2, free fatty acids, and others. According to I.L. Loktionova and co-authors, there are three main stimuli that cause a hormonal response from the endothelial cell. These are changes in blood flow (velocity), platelet mediators, and catecholamines, vasopressins, acetylcholines, endothelins, bradykinins, and histamines [8].

In patients with CKD, the prerequisites for vascular endothelial dysfunction appear in the early stages of the disease and progress as the GFR decreases. As mentioned above, endothelial dysfunction refers to an imbalance between procoagulant and anticoagulant factors, which disrupts relaxation, vasoconstriction, and hemovascular homeostasis. A primary characteristic of endothelial dysfunction is the insufficient production of nitric oxide (NO). The NO compound is a potent endogenous vasodilator synthesized from L-arginine with the help of NO synthase [14, 15]. In turn, NO synthase exists in isoforms such as neuronal NO synthase (nNOS, NOS-I), inducible NO synthase (iNOS, NOS-II), and endothelial NO synthase (eNOS, NOS-III). It should be noted that eNOS is consistently expressed in endothelial cells, including the epithelium of the renal tubules [8].

According to data in the literature, there are two levels of eNOS secretion: basal and stimulated. At rest, vascular tone is maintained by basal secretion. In this state, NO regulates the basal tone of systemic, coronary, and pulmonary vessels by inhibiting endothelin-1 synthesis and limiting the release of norepinephrine from sympathetic nerve endings. An increase in the stimulated secretion of eNOS activates intracellular calcium levels and intracellular guanylate

cyclase [8]. NO diffuses into the smooth muscle cells of the vessels, activating guanylate cyclase and leading to the formation of cyclic guanosine monophosphate. This results in vasodilation. Furthermore, NO slows the proliferation of smooth muscle cells, prevents the oxidation of LDL, and inhibits the aggregation and adhesion of platelets and leukocytes to endothelial cells [8].

NO inhibits the expression of pro-inflammatory genes in the vascular wall, particularly the transcription factor nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB). In the early stages of CKD, impaired endothelium-dependent vasodilation in patients is associated with high serum levels of annexin A5 and daily sodium chloride excretion [8]. A number of studies indicate that endothelial dysfunction is observed in children with CKD from the very first stage of the disease. This should be considered a determining factor in the progression of the pathological process in the kidneys [6, 7]. As CKD progresses, NO secretion decreases significantly. This is accompanied by a considerable reduction in the NO/endothelin-1 ratio, a predominance of the vasopressor endothelin-1, and the development of endothelial dysfunction. The increase in serum endothelin-1 levels with the progression of CKD signifies vasoconstriction during the initial stages of nephrosclerosis [9].

Additionally, in adult patients with CKD, endothelial nitric oxide (NO) production is diminished due to decreased NO synthase activity resulting from arterial hypertension (AH), atherogenic dyslipidemia, and hyperglycemia. It should be noted that against the backdrop of reduced NO synthesis, a tendency towards vasoconstriction is observed, which increases the prothrombogenic potential of blood in the tissues. This leads to microthrombosis in the renal glomeruli. Over time, the elasticity of blood vessels decreases, and their compliance is reduced due to a disruption in the relationship between elastin and collagen fibers [3]. This process results in the breakdown of elastin fibers, which are then replaced by collagen fibers, creating a rigid structure that sustains persistent hypertension. Furthermore, the reduced bioavailability of NO is characterized by diffuse thickening of the arterial intima-media complex and vascular calcification [8]. Concurrently, over time, increased oxidative stress and active, persistent inflammation further decrease endothelial NO levels, all of which contribute to the development of endothelial dysfunction [13].

In patients with CKD, endothelial dysfunction, structural and functional changes in the vascular walls, and the secretion of vasoconstrictors disrupt the autoregulation of blood flow in the kidneys. N.V. Kuzminova and V.K. Serkova recognized that a change in blood flow velocity leads to a change in the lumen of large arteries: that is, arteries dilate as blood flow increases and constrict as it decreases. This regulation of arterial diameter is a local process and is not determined by nervous or humoral effects on smooth muscle tone. The sensitivity of arteries to blood flow velocity is explained by the ability of endothelial cells to sense the shear stress exerted on them by the flowing blood. This leads to their flow-dependent deformation. This deformation is sensed by the stretch-sensitive ion channels of the endothelium, which leads to an increase in cytoplasmic calcium levels and the release of NO [8]. On the other hand, in small-diameter arteries, an increase in blood flow velocity in an area of vascular narrowing (e.g., atherosclerotic plaque, stenosis) leads to platelet activation. This compensatorily leads to platelet adhesion to the impaired endothelium and intravascular thrombus formation. It should be noted that the mechanism of platelet adhesion to damaged endothelium differs at varying flow velocities. At low velocities (at the level of large vessels), platelet adhesion occurs directly to subendothelial collagen. At high velocities, the necessary interaction between platelets and the vessel wall occurs, which is mediated only with the participation of the von Willebrand factor [8]. In elderly and senile patients with CKD, vascular changes occur not only in large vessels but also in the microcirculatory network. There is evidence that in these patients, endothelial dysfunction occurred long before the development of renal structural changes, which play a significant role in the formation of microcirculatory disorders in the kidneys [10].

E.V. Polukhina (2015) analyzed the relationship between endothelial dysfunction and disorders of calcium-phosphorus metabolism, along with an assessment of endothelial function based on ultrasound data in 200 patients with various stages of CKD. A high prevalence of endothelial dysfunction was identified in CKD patients. This was particularly observed in patients undergoing scheduled hemodialysis [8]. It was noted that endothelial dysfunction is more pronounced in patients with arterial hypertension, dyslipidemia, disorders of calcium-phosphorus metabolism, and vascular calcification [10].

In a study by A.B. Susla of 167 patients in the pre-dialysis stage of CKD, the role of endothelial dysfunction in carotid artery calcification was determined by studying indicators of endothelial vasomotor function, the content of stable NO metabolites, and the number of circulating endothelial cells.

It was reported that in these patients, calcification of carotid plaques occurred in conjunction with endothelial damage, impaired vasoreactivity, and NO deficiency. The author emphasizes that the presence of a complex of structural and functional endothelial disorders indicates the need to initiate endothelial protective therapy in these patients with carotid artery calcification [8].

Changes in blood vessel diameter, which depend on age and a number of other factors, are of particular clinical and functional importance in this context. According to the literature, small-diameter arteries branch into precapillaries and capillaries, delivering blood to the renal tissues to satisfy metabolic needs [5]. They enable the optimal maintenance of the organ's basic functions, including the GFR [8]. The structural remodeling of an interlobular artery is an important criterion indicating an increased likelihood of developing glomerulosclerosis [5]. In middle-aged and older adults, systemic arterial hypertension, hyper- and dyslipidemia, and persistent hyperglycemia lead to the remodeling of renal arteries. Previously published studies have demonstrated the role of increased peripheral renal resistance in the remodeling process of arteries with a diameter of less than 0.3 mm, which occurs against a background of slightly elevated and even normal systemic arterial pressure, with subsequent involvement of the renal parenchyma in the pathological process [5]. Subsequent studies have shown a relationship between arterial hypertension and the thickness of the interlobular artery wall, as well as the intimal layer of the vessels. As scientists have noted, the hypertrophy of interlobular arteries becomes particularly significant when blood pressure exceeds a certain level [5]. The remodeling of small-diameter renal arteries is certainly accompanied by the narrowing of their lumen. The cited studies noted a correlation between the narrowing of the interlobular artery lumen and the development of glomerulosclerosis [5]. From this perspective, particularly in older groups of CKD patients, disorders in lipid and carbohydrate metabolism, oxidative stress, anemia, and inflammation in small-diameter arteries stimulate neoangiogenesis. At this point, endothelial dysfunction leads to impaired renal tissue perfusion and the activation of their remodeling processes.

E. S. Levitskaya et al. (2017) suggest that with the thickening of the interlobular artery wall, the risk of capillary wall thickening, generalization of capillary loops, and their obliteration increases. In their view, tissue and vascular remodeling should be considered an interrelated process underlying the development of kidney diseases [5]. In this context, pathological changes in the small-diameter renal arteries are of particular interest. This is because these structures are not only convenient for morphological assessment during a kidney biopsy but also actively influence the state of the nephron.

Increased production of transforming growth factor-beta (TGF-β) leads to a decrease in the muscular-type elasticity of the arteries. This is accompanied by an exacerbation of endothelial dysfunction and impaired intraglomerular microcirculation. High consumption of table salt is also associated with increased production of TGF-β and NO by endothelial cells [8]. It is evident that the endothelium plays a crucial role in regulating vascular architecture, and long-term changes in hemodynamic stress can mediate vascular remodeling through alterations in vascular wall components, including endothelial cells, smooth muscle cells, and the collagen matrix. A healthy endothelium maintains the luminal surface of intact vessels and governs antithrombotic, fibrinolytic, and anticoagulant mechanisms [8].

Thus, in modern clinical medicine, the endothelium is regarded as a large and active endocrine organ that participates in many physiological and pathological processes in the body. Endothelial dysfunction is accompanied by a number of pathomorphological, pathochemical, and pathophysiological changes in the body. This often forms the basis of the disease's extensive pathogenetic mechanisms. Endothelial dysfunction is one of the most fundamental pathogenetic mechanisms important in the development and progression of CKD. Therefore, in current nephrology practice, diagnosing endothelial dysfunction and coordinating it with the necessary therapy is the most optimal way to slow the progression of chronic renal failure.

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