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The Importance of Clotho Proteinin the Development of Chronic Kidney Disease in the Context of Chronic Heart Failure

Djuraeva Nozima Orifovna
Bukhara State Medical Institute, Uzbekistan, Bukhara
djurayeva.nozima@bsmi.uz

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Annotation: The review article presents current research data on the importance of the Clotho proteinin the pathogenesis of chronic kidney disease in the context of chronic heart failure. The relationship of the Clotho protein with fibroblast growth factor–23 and its antioxidant properties is presented. It has been describedthat the α–clotho protein reduces the development of endothelial dysfunction and atherosclerosis by reducing oxidative stress and inflammation.

Keywords: Clotho protein, chronic kidney disease, chronic heart failure, antioxidant system, fibroblast–23.

Relevance. Heart and kidney diseases are widespread pathological processes among the population, treatment is complex and expensive, with severe complications and leads to death.

Currently, there are a number of grounds for the significance of common factors in the mechanisms of their development. From a pathophysiological point of view, damage to the heart and kidneys (cardiorenal syndrome) is a combined dysfunction of both organs, manifested by the progression of their insufficiency[1].

In the mechanism of development of chronic renal disease against the background of chronic heart failure, hemodynamic disorders, neurohumoral activation, endothelial dysfunction, atherosclerosis, an increase in inflammatory cytokines, oxidative stress, embolism of renal vessels, and other factors are significant [2].

In recent years, scientific works devoted to studying the influence of Kloto protein on kidney function and the course of hypertension have aroused interest among many scientists. The cloto protein gene was first identified in 1997. Klotho (Eng. Klotho) - a transmembrane protein, β-glucuronidase, interacting with several receptors in the human body, balancing insulin sensitivity. This protein has three subfamilies (α-klotho, β-klotho, and γ-klotho), α-klotho is

synthesized in the human brain, liver, and kidneys, β-klotho is mainly synthesized in the liver, and γ-klotho is synthesized in the skin. It is released directly into the intercellular space and is present in all biological fluids, such as blood, cerebrospinal fluid, and urine. With age, the amount of Kloto protein decreases. In patients with chronic kidney disease (CKD), a decrease in the production of this protein is observed, as a result of which degenerative processes (such as atherosclerosis, osteoporosis, and skin atrophy) develop early and progress rapidly [13,19,20].

The clotho gene is located in kidney tissue and mainly carries out the synthesis of the α-klotho protein. This protein plays an important role in controlling phosphate levels in the human body. The amount of phosphates in the body is controlled by the kidneys. In healthy people, excess phosphates are excreted in the urine, and when more is needed, the mineral is reabsorbed into the blood [19,20]. It was established that there is an inverse correlation between the concentration of cloto protein in blood serum and complications of cardiovascular diseases. At the same time, in some scientific works, a correlation has been observed between its decrease and deterioration of kidney function [20].

Klotho protein has a molecular weight of 130 kDa and consists of 1014 amino acids. It has N-terminal and short cytoplasmic domain with transmembrane domain step-by-step signal transmission to C terminal. The extracellular domains of the clotony consist of two internal repeats of KIM-1 and homologous step-by-step β-glycosidases[3]. Three members of the transmembrane Klotho protein of different lengths have been identified in the mammalian genome. The α-klotho can be obtained using transmembrane β-secretase, which is soluble.

In recent years, there has been a great interest in the study of the new cloto protein. Professor Makoto Kuno recently discovered an autosomal recessive mutation in the kloto gene. [4]. Klotho protein is released directly into the extracellular space and is present in biological fluids such as blood, cerebrospinal fluid, and urine [5]. Klotho protein belongs to the class of hormonal proteins, it determines the functions and state of many metabolic processes and many ion channels, the activity of a number of organs - the parathyroid gland, liver, heart, pancreas [6]. After the discovery of the cloto gene and its protein, it was found that its largest amount is localized in the kidneys, in connection with which the main part of scientific research is devoted to the problem of "cloto protein and kidneys" [7].

Polymorphisms of the Kloto gene and the association of its protein with cardiovascular pathology are currently of great scientific interest and are being actively studied [8]. A number of experimental publications have suggested that clotho protein can reduce oxidative stress and inflammation. According to scientific publications, a lack of clotho protein in the blood increases the formation of endogenous reactive oxygen species and intensifies oxidative stress [9]. In addition, its protective properties in the vascular wall are associated with an improvement in the function of endothelium and fibroblasts [10], a decrease in inflammatory processes. Klotho protein plays an important role in the regulation of phosphorus-calcium metabolism, a decrease in Klotho protein in the blood may be associated with the development of vascular calcification [11]. Clinical studies have shown that a low level of clotho protein is associated with an increase in the incidence of coronary heart disease and the severity of atherosclerotic lesions of the arteries. The participation of cloto protein in regulating nitric oxide production and inhibiting many proteins, such as angiotensinogen, renin, angiotensin-converting enzyme, and type 1 angiotensin inhibitor receptors, can have a significant impact on blood pressure [12].

Klotho protein is produced in most organs, but most often in the kidneys. It is secreted in large quantities from the proximal and distal tubules of the kidney, as well as from the epithelial cells of the parathyroid gland [13].

The possibilities of using clotho as a biomarker of CKD have been studied by some researchers. High morbidity and mortality from cardiovascular diseases are indicated in the terminal stage of CKD [13]. Disorders of mineral metabolism include elevated levels of phosphates, fibroblast-23, and parathyroid hormone in blood serum, which are closely related to clotho protein deficiency

[14]. Clinical studies conducted in patients with CKD revealed that in patients with CKD, the indicators of soluble clotes were below normal (845±330 pg/ml versus 519±183, P<0.0001). The soluble clotho has a positive correlation with serum calcium and a negative correlation with phosphate, parathyroid hormone, and fibroblast-23. Consequently, the soluble clotho can be an early marker of CKD and mineral changes in bones. In addition, there is information that fibroblast-23 reflects the resistance of the renal tubules [15]. Consequently, soluble clotho can be used as a marker of phosphate and bone tissue metabolism disorders in chronic kidney disease[16].

The glomerular filtration rate (GFR), which is considered the gold standard for assessing the function of this organ in CKD, decreases according to its severity. Clinical and experimental studies have shown that a significant decrease in the level of glucose protein in the blood has a positive correlation with eGFR in CKD [17]. Several other studies have also confirmed a positive correlation between the level of clotho (in blood serum and urine) and eGFR in older patients with CKD [18].

However, some data suggest that the level of clotho protein in blood serum and urine is not associated with eGFR in patients with CKD [19].

In another study, in parallel with the development of CKD, the level of clotho protein in blood serum gradually decreases. In this case, a corrected average GFR of 1.73 m2 per 1 minute corresponded to a decrease in protein by 3.2 pg/ml [20].

However, Sara Seiler et al., analyzing a large group of 312 patients with stage 2-4 CKD, found that there was no reliable correlation between plasma cloto protein and eGFR and other indicators of calcium-phosphorus metabolism [21]. There may be two reasons for this contradictory information. One of them is young. Yamadzaki et al. hypothesized that the level of soluble clotho protein is age-dependent and found that clotho levels are higher in children (average age 7.1±4.8 years) than in adults[22]. Simamura et al. also reported a significantly lower level of clotho protein in patients with stage 2-5 CKD compared to patients with stage 1 CKD [23].

α-klotho reduces the rate of apoptosis in endothelial cells, resulting in increased nitric oxide (NO) secretion and improved endothelial vasodilation and antithrombotic function[24].

Conclusion

1. The conducted analyses confirm that chronic heart failure and kidney damage in it is one of the most common pathological conditions in the world. The obtained data and conclusions allow for early diagnosis of renal dysfunction in patients with chronic heart failure, preventing the development of CKD, improving the quality of life and extending the life expectancy of patients, as well as preventing sudden death.

2. In the early diagnosis of exacerbation of chronic heart failure and kidney damage as a result of this disease, Kloto protein, along with generally accepted tests, is of great importance. Taking into account the above, it is advisable to conduct additional scientific research in this area.

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