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Main Role Of Morphogenetic Between Fgf-23 And Sklotho In The Development Of Herdic And Vasicular Models In Chronic Key Disease Patients

Nodira Mirshavkatovna Alikhanova
Doctor Of Medical Sciences, Republican Scientific-Practical Medical Center Of Endocrinology Of The Ministry Of Health Of The Republic Of Uzbekistan

Aikhojaeva Mokhira Akmalovna
Candidate Of Medical Sciences, Republican Scientific-Practical Medical Center Of Endocrinology Of The Ministry Of Health Of The Republic Of Uzbekistan

Nazarova Nozimakhon Sunnatilla Kizi
1 Year Basic Doctoral Student, Republican Scientific-Practical Medical Center Of Endocrinology Of The Ministry Of Health Of The Republic Of Uzbekistan

Charos Bakhtiyorovna Musakhanova
Endocrinologist In The Department Of Diabetic Nephropathy, Republican Scientific-Practical Medical Center Of Endocrinology Of The Ministry Of Health Of The Republic Of Uzbekistan

ABSTRACT

Diabetes is a major cause of chronic kidney disease (CKD). Poor blood sugar control accelerates the progression of CKD to terminal renal failure. Chronic kidney disease is also an important co-morbidity of diabetes. Impaired renal function further increases the risk of cardiovascular events in diabetic patients and ultimately carries a severe social and economic burden. Altered fibroblast growth factor 23 (FGF-23) and Klotho levels are considered the earliest biochemical abnormality of chronic kidney disease, the mineral and bone disease syndrome.

KEYWORDS

Cardiovascular disease, chronic kidney disease, fibroblast growth factor-23, Klotho, uremic vasculopathy.

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INTRODUCTION

Among the urgent problems of practical public health care, the leading place is occupied by prevention and treatment of cardiovascular diseases, which are the main cause of death among the population [1,2]. At the same time, chronic kidney disease (CKD) as one of the widespread population diseases, having not only general medical, but also social and economic significance, attracts close attention of researchers in terms of the frequency of cardiovascular complications (CVD), as patients with CKD die more often from cardiovascular causes than from renal failure [3], however traditional cardiovascular risk factors such as tobacco smoking, arterial hypertension and hypercholesterolemia do not explain this high mortality rate . Mortality from CVCs among patients with CKD is 10 times higher, and among young adults 100 times or more, than in the general population. Myocardial remodeling and vascular calcinosis are the main manifestations of cardiovascular morbidity and independent risk factors of death in CKD. Calcium deposition in the vessels poses a particularly high risk of mortality from cardiovascular complications and all-cause mortality [2]. Approximately 40% of patients with pre-dialysis stages of CKD and over 80% of patients starting hemodialysis (HD) treatment show left ventricular hypertrophy (LVH) [4,5]. Arterial calcification develops before patients reach dialysis, and significant manifestations are seen in more than 60% of patients who first begin hemodialysis (HD) treatment, reaching 83-100% in patients on long-term HD [1,5].

Altered fibroblast growth factor 23 (FGF-23) and Klotho levels are considered to be the earliest biochemical abnormality of chronic kidney disease, the mineral and bone disease syndrome . Moreover, emerging evidence suggests that dysregulation of FGF-23 and the Klotho axis has multiple effects on the cardiovascular (CV) system and contributes significantly to the increased incidence of cardiovascular disease and mortality in patients with CKD. This review explores recent evidence on the role of FGF-23 and Klotho in the development and progression of cardiovascular complications of uremia, namely cardiac hypertrophy, uremic cardiomyopathy, and atherosclerotic and arteriosclerotic vascular lesions. Moreover, the available evidence of their association with adverse clinical outcomes is summarized. Undoubtedly, additional studies are needed to further elucidate the effects of FGF-23 and Klotho on heart and blood vessels and to understand their prognostic value as cardiovascular risk factors. Finally, large prospective studies are needed to test the hypothesis that changing their levels would have a beneficial effect on the unacceptably high mortality rates of these patient groups.

α-Klotho (Klotho) exists in two different forms, namely in membrane-bound and soluble forms, which are highly expressed in the kidneys. Both forms play important roles in various physiological and pathophysiological processes. Recently, it has been determined that soluble Klotho is only produced by shedding or proteolytic cleavage.

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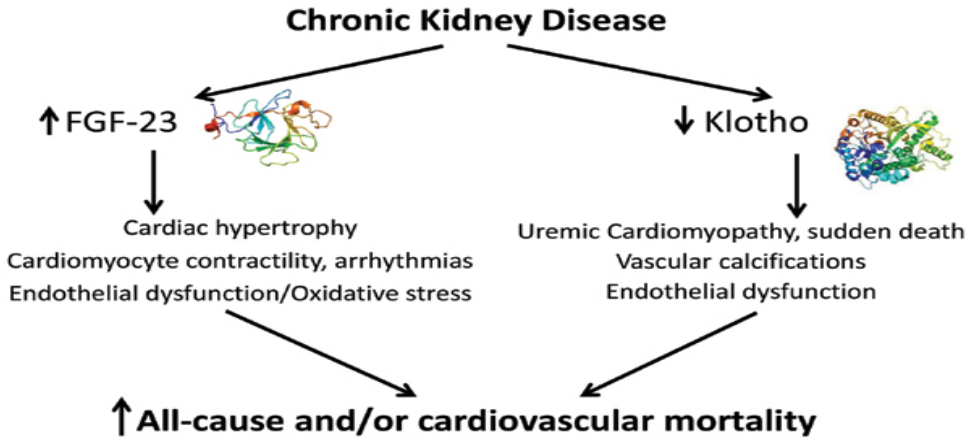

M10 and ADAM17 are the main cause of this saddling, leading to the formation of full-length fragments or subfragments called KL1 and KL2. Decreased soluble Kloth is associated with kidney disease, especially chronic kidney disease (CKD). Consistent with the protective effect of soluble Klotho on vascular function and calcification, decreased CKD and soluble Klotho levels in this article are associated with cardiovascular complications.

The CKD-MBD syndrome includes biochemical changes in mineral metabolism, impaired skeletal remodeling, and extracellular calcinosis that develop when glomerular filtration decreases by more than 40%. When defining the concept of CKD-MBD syndrome related to the study of cardiovascular risk factors, the following features are considered: changes in phosphorus content [10]; abnormalities in fibroblast growth factor 23 (FGF23) content [11]; the presence of vascular calcinosis [12]. Among persons with CKD not receiving dialysis, increased peripheral arterial stiffness, vascular calcification, and cardiac valve calcification are clearly associated with higher serum Pi concentrations [13- 16]. In the Coronary Artery Risk Development in Young Adults (CARDIA) study, the risk of coronary artery calcification in young adults with serum Pi levels greater than 3.9 mg/dL increased by 52% (compared with 3.3 mg/dL) after 15 years of prospective follow-up [22]. Calcium deposition in blood vessels poses a particularly high risk of mortality from CVCs [18]. Considering that calcinosis is considered as a component of aging, the increased cardiovascular risk is especially common in CKD. On this basis, we searched for early markers of CVC development in patients with CKD, which revealed a functional role of morphogenetic proteins FGF-23 and Klotho (sKlotho), including as humoral factors, involved in the processes of cardiac and arterial vascular remodeling in CKD [19,20], although for the first time these proteins were studied only from the position of their participation in the regulation of mineral and bone metabolism in this disease [9]. Increased formation of FGF23 and decrease of its coreceptorKlotho are typical signs of persistent positive Pi balance in patients with renal dysfunction.Impaired renal nitrogen excretion is a potential state of Klotho deficiency due to a decrease in its concentration in both the tissue and the circulatory system. In this case, it is important to clarify whether Klotho deficiency contributes to reduced life expectancy and other many severe complications in patients with CKD with an increase in cardiovascular

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complications and death. In addition to decreased GFR, other factors of increased systemic FGF23 levels are the traditional predictors of cardiovascular risk - age, smoking, obesity, arterial hypertension, diabetes mellitus, and inflammation [21-23]. Numerous observations indicate an association between circulating FGF23 levels and the risk of adverse cardiovascular events in CKD [23-27]. There is evidence for FGF23 as a cardiovascular risk factor in the general population, with even moderate increases in FGF23 shown to be associated with major adverse events in individuals without significant renal dysfunction [28,29]. Elevation of FGF23 is considered as a population risk factor determining the risks of cardiovascular events independently of traditional risk factors, other indicators of calcium-phosphate metabolism, as well as myocardial mass and arterial wall condition in patients without a clear decrease in FFR [29,30]. The increase in risk with increased FGF23 is also mediated by the progression of myocardial hypertrophy and dysfunction [31,32]. A three-year follow-up study of patients with CKD showed a 4.5-fold increase in the risk of decompensated heart failure and/or cardiac death among those with FGF23 levels within the third tertile compared with those in whom they corresponded to the first tertile [33]. Increased FGF23 levels have been found to develop earlier than increases in phosphorus and parathyroid hormone (PTH) levels [34,35]. FGF-23 is a phosphaturic hormone that maintains normal serum phosphorus concentrations in patients with CKD by increasing urinary excretion of phosphorus and decreasing its absorption from the GI tract - a result of inhibition of 1,25-dihydroxyvitamin D synthesis. At the same time, increased serum levels of FGF-23 have been found to be associated with endothelial dysfunction, HLV, and increased cardiovascular mortality [36,37].These results provide an opportunity to consider FGF-23 as a new marker of cardiovascular risk in CKD. Currently, there is evidence that most of the pathological effects of FGF-23 may be due to the deficiency of another factor, Klotho, in the progression of CKD. It is known that the mediator for FGF23 in the vascular wall is Klotho, an evolutionarily conserved protein associated with longevity, which was discovered in 1997 by Kuro-o [18]. The name Klotho is related to Greek mythology, where Klotho is one of the fates that spins the thread of human life. Phenotypes of experimental models of reduced Klotho gene expression, are characterized by systemic manifestations of accelerated aging and premature death, and homeostatic shifts correspond to Pi metabolic disorders in CKD patients - hyperphosphatemia, FGF23 increase, development of hyperparathyroidism, osteopenia, vascular calcification. Experimental and Clinical Medicine The systemic cardiovascular effects of FGF23 and Klotho interaction may be mediated by activation of the renin-angiotensin system due to reduced calcitriol formation and suppression of the angiotensin convertase 2 gene [39]. The main site of FGF23 production is osteocytes, and Klotho protein - renal tubules and parathyroid glands [40]. There is an assumption about the role of FGF23 and Klotho receptor interaction in physiology and pathology of cardiovascular system, although the significance of local expression of these molecules in cardiovascular system remains a subject of study. It has been noted that increased Klotho activity significantly inhibits vascular calcification processes in experimental models of CKD [41] and they indicate that Klotho can attenuate the negative functional vascular effects induced by FGF23 [42]. It is important to clarify whether Klotho deficiency contributes to reduced life expectancy and many other severe complications in patients with CKD with increased cardiovascular complications and

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death. Decreased serum and urine Klotho levels followed by increased serum FGF23 levels in early-stage CKD serve as an early biomarker of impaired renal function and may also be a predictor of cardiovascular risk and mortality both in patients with CKD and in the general population. Thus, sKlotho protein, in addition to its role in regulating calcium and phosphorus metabolism, has cardioprotective effects because its deficiency is associated with increased cardiovascular morbidity and mortality. Understanding the early mechanisms of arterial calcification and VLDL is necessary to develop new therapeutic approaches to reduce cardiovascular morbidity and preserve survival in patients with CKD. Based on the above, the study of mineral-bone abnormalities in CKD using the morphogenetic proteins FGF-23 and s Klotho is an important area of research of practical importance for modern healthcare, as it establishes a new cluster of cardiovascular risks. Evidence of the protective effect of Klotho protein on blood vessels may play an important role in the treatment and prevention of cardiovascular complications in patients with CKD. As a consequence, the potential modifiability of phosphorus-calcium metabolism imbalance factors may become the basis for the development of a separate direction of cardiovascular prevention, which seems important in theoretical and practical terms.

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