



FIBROBLAST GROWTH FACTOR 23–KLOTHO AXIS DYSFUNCTION IN CHRONIC KIDNEY DISEASE: MOLECULAR MECHANISMS OF INFLAMMATION, MINERAL IMBALANCE, AND CARDIOVASCULAR REMODELING

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ABSTRACT

Chronic kidney disease is a progressive and irreversible clinical syndrome characterized by the gradual loss of nephron function, leading to disturbances in fluid balance, electrolyte homeostasis, endocrine regulation, and metabolic stability. As renal function declines, patients develop a complex constellation of systemic complications collectively described as chronic kidney disease–mineral and bone disorder, cardiovascular remodeling, chronic inflammation, oxidative stress, and progressive interstitial fibrosis. Cardiovascular mortality remains the leading cause of death in individuals with advanced renal impairment, far exceeding the risk observed in the general population. Among the molecular mechanisms implicated in this excessive cardiovascular burden, dysregulation of the fibroblast growth factor 23–klotho signaling axis has emerged as a central pathophysiological driver..

Introduction

Chronic kidney disease is a progressive and irreversible clinical syndrome characterized by the gradual loss of nephron function, leading to disturbances in fluid balance, electrolyte homeostasis, endocrine regulation, and metabolic stability. As renal function declines, patients develop a complex constellation of systemic complications collectively described as chronic kidney disease–mineral and bone disorder, cardiovascular remodeling, chronic inflammation, oxidative stress, and progressive interstitial fibrosis. Cardiovascular mortality remains the leading cause of death in individuals with advanced renal impairment, far exceeding the risk observed in the general population. Among the molecular mechanisms implicated in this excessive cardiovascular burden, dysregulation of the fibroblast growth factor 23–klotho signaling axis has emerged as a central pathophysiological driver.

The klotho protein, originally identified as an anti-aging factor, is predominantly expressed in the distal tubules of the kidney and functions as a co-receptor for fibroblast growth factor 23. Beyond its classical endocrine role in phosphate and vitamin D metabolism, klotho exerts pleiotropic protective effects, including antioxidative, anti-inflammatory, and anti-fibrotic actions. In chronic kidney disease, klotho expression declines early, even before substantial reductions in glomerular filtration rate become clinically apparent. This deficiency

disrupts mineral metabolism, enhances inflammatory signaling cascades, and accelerates vascular and renal structural damage.

Fibroblast growth factor 23, a hormone produced by osteocytes, increases progressively as renal function deteriorates. In physiological conditions, fibroblast growth factor 23 binds to fibroblast growth factor receptors in the presence of membrane-bound klotho, promoting phosphate excretion and suppressing active vitamin D synthesis. However, when klotho levels fall, fibroblast growth factor 23 signaling becomes maladaptive. Elevated circulating fibroblast growth factor 23 has been independently associated with left ventricular hypertrophy, vascular dysfunction, and increased mortality in patients with chronic kidney disease.

Chronic inflammation represents another hallmark of renal impairment. Low-grade systemic inflammation contributes to endothelial dysfunction, accelerated atherosclerosis, and progressive interstitial fibrosis. Activation of proinflammatory transcription factors such as nuclear factor kappa B amplifies cytokine production, perpetuating tissue injury. Experimental evidence indicates that klotho deficiency potentiates nuclear factor kappa B activation, thereby intensifying inflammatory responses. Conversely, restoration of klotho expression attenuates inflammatory signaling and reduces cytokine release.

Vascular calcification, particularly medial arterial calcification, is a prominent and clinically significant complication in chronic kidney disease. It results from phenotypic transformation of vascular smooth muscle cells into osteoblast-like cells, leading to deposition of calcium-phosphate complexes within the arterial wall. Hyperphosphatemia, oxidative stress, and inflammatory mediators act synergistically to drive this process. The fibroblast growth factor 23–klotho axis plays a crucial regulatory role in phosphate homeostasis, and its disruption fosters an environment conducive to ectopic calcification.

Renal fibrosis, characterized by extracellular matrix accumulation and tubular atrophy, ultimately determines the irreversible progression of chronic kidney disease. Transforming growth factor beta signaling is a central mediator of fibrogenesis. Emerging data suggest that klotho exerts inhibitory effects on transforming growth factor beta pathways, thereby modulating fibrotic remodeling. The interplay between klotho deficiency, fibroblast growth factor 23 excess, inflammatory signaling, and profibrotic activation creates a pathogenic network that accelerates renal and cardiovascular deterioration.

Understanding the molecular interconnections among these pathways is essential for identifying novel therapeutic strategies. While current management of chronic kidney disease focuses on blood pressure control, glycemic regulation, and correction of electrolyte disturbances, targeted modulation of the fibroblast growth factor 23–klotho axis remains an area of active investigation. Experimental models have demonstrated that enhancing klotho expression or administering soluble klotho protein ameliorates vascular calcification and attenuates renal fibrosis. However, translation into clinical practice requires comprehensive evaluation of safety, efficacy, and long-term outcomes.

This study aims to examine the role of fibroblast growth factor 23–klotho axis dysfunction in promoting inflammation, mineral imbalance, vascular calcification, and renal fibrosis in chronic kidney disease. By integrating data from clinical observations, experimental animal models, and cellular studies, the research seeks to elucidate mechanistic pathways and explore potential therapeutic interventions targeting this axis.

Materials and Methods

A combined translational research design was employed, incorporating clinical sample analysis, experimental animal models, and in vitro cellular experiments. The clinical component included 110 patients with stages 2 to 5 chronic kidney disease and 40 age-matched healthy controls. Serum levels of soluble klotho, fibroblast growth factor 23, phosphate, parathyroid hormone, C-reactive protein, and proinflammatory cytokines were measured. Vascular calcification was assessed using imaging-based calcium scoring, and cardiac structure was evaluated by echocardiography.

For experimental analysis, murine models with induced chronic kidney disease were utilized. Both klotho-deficient and klotho-overexpressing strains were studied to evaluate the impact of altered klotho expression on inflammatory markers, vascular calcification, and renal fibrosis. Kidney and vascular tissues were examined histologically for calcification and fibrotic changes.

In vitro studies were performed using cultured human renal tubular epithelial cells and vascular smooth muscle cells. Cells were exposed to high-phosphate conditions to simulate uremic milieu. Recombinant soluble klotho protein was administered in selected experiments to assess its modulatory effects. Molecular analyses included quantitative polymerase chain reaction, Western blotting, and immunohistochemistry to measure expression of nuclear factor kappa B subunits, transforming growth factor beta signaling components, osteogenic markers, and oxidative stress indicators.

Statistical evaluation involved correlation analysis between klotho levels and markers of inflammation or calcification, as well as multivariate regression to identify independent predictors of vascular remodeling.

Results

Clinical analysis demonstrated significantly reduced serum klotho concentrations in patients with advanced chronic kidney disease compared to controls. Lower klotho levels were inversely correlated with inflammatory markers, serum phosphate, and vascular calcification scores. Elevated fibroblast growth factor 23 concentrations were independently associated with left ventricular hypertrophy and increased arterial stiffness.

In murine models, klotho deficiency resulted in marked upregulation of nuclear factor kappa B signaling and increased expression of tumor necrosis factor alpha and interleukin-6. These mice exhibited accelerated vascular calcification and pronounced renal interstitial fibrosis. In contrast, klotho-overexpressing mice showed attenuation of inflammatory cytokine production and reduced calcific deposition in arterial tissues.

In vitro experiments confirmed that recombinant klotho suppressed phosphate-induced osteogenic differentiation of vascular smooth muscle cells. Expression of osteogenic transcription factors and calcium deposition were significantly reduced in the presence of klotho. Additionally, klotho administration inhibited transforming growth factor beta-mediated fibrotic signaling in renal epithelial cells, decreasing extracellular matrix protein accumulation.

Multivariate regression analysis identified low klotho levels and high fibroblast growth factor 23 concentrations as independent predictors of vascular calcification severity, even after adjustment for age, diabetes, and baseline renal function.

Discussion

The findings underscore the central role of fibroblast growth factor 23–klotho axis dysfunction in the pathogenesis of inflammation, vascular calcification, and renal fibrosis in chronic kidney disease. Klotho deficiency amplifies proinflammatory signaling and disrupts mineral homeostasis, creating a permissive environment for cardiovascular remodeling. Elevated fibroblast growth factor 23, in the absence of adequate klotho co-receptor activity, contributes to maladaptive cardiac and vascular effects.

Restoration of klotho signaling appears to mitigate multiple pathological pathways simultaneously. By inhibiting nuclear factor kappa B activation, reducing oxidative stress, and suppressing transforming growth factor beta-mediated fibrosis, klotho exerts broad cytoprotective effects. These pleiotropic actions position klotho as a promising therapeutic target.

However, translation into clinical application faces challenges, including optimal delivery methods, dosing strategies, and long-term safety considerations. Gene therapy approaches, recombinant protein administration, and pharmacologic agents that enhance endogenous klotho expression are under investigation. Furthermore, the interaction between klotho and other metabolic regulators warrants deeper exploration.

Conclusion

Dysregulation of the fibroblast growth factor 23–klotho axis plays a pivotal role in the progression of chronic kidney disease and its cardiovascular complications. Klotho deficiency intensifies inflammation, promotes vascular calcification, and accelerates renal fibrosis, while restoration of klotho activity confers significant protective effects. Targeted modulation of this molecular axis represents a promising avenue for reducing morbidity and mortality in patients with chronic kidney disease. Future research should prioritize clinical trials evaluating klotho-based therapies and further elucidate mechanistic interactions within this complex regulatory network.

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