Klotho and The Kidney

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Abstract

Klotho has emerged as one of the most important renoprotective proteins linking kidney function with systemic metabolic, endocrine, and cardiovascular health. Predominantly expressed in the renal tubules, Klotho regulates phosphate homeostasis through the fibroblast growth factor-23 (FGF23) pathway while exerting pleiotropic effects on oxidative stress, inflammation, fibrosis, mitochondrial function, and cellular senescence. Declining Klotho expression is a hallmark of chronic kidney disease (CKD) and contributes to mineral bone disorder, vascular calcification, accelerated ageing, and progressive renal dysfunction. Beyond serving as a biomarker of kidney health, Klotho represents a promising therapeutic target capable of enhancing renal resilience and slowing disease progression. Lifestyle interventions, particularly regular exercise, together with emerging pharmacological strategies, may preserve endogenous Klotho expression and contribute to nephroprotection. As nephrology evolves toward a cardiorenal-metabolic paradigm, Klotho provides a unifying biological framework connecting the kidney with multiple organ systems. Future research into Klotho-based diagnostics and therapeutics may transform the prevention and management of CKD and its systemic complications.

Keywords: Ageing, Cardiorenal syndrome, Chronic kidney disease, Exercise, Fibroblast growth factor 23, Mineral metabolism, Vascular calcification.

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Introduction

The retroperitoneal kidneys have long been viewed as secretive organs, meant just for filtration and excretion. Yet, in the modern era of cardiorenal medicine, this is an incomplete portrait. Klotho has emerged as one of the most provocative molecules in nephrology, reminding us that the kidney is also an endocrine, immunologic, and metabolic organ[1]. Klotho modulates renal aging, mineral metabolism, vascular health, oxidative stress, and the systemic consequences of chronic kidney disease. Prompted by exercise, and produced by the kidneys, klotho represents the healing power of the kidneys. The protein transforms the kidneys from villains and victims of metabolic health to virtuous knights of health[1-3].

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Klotho

Klotho is as a longevity-related protein, found in at least two isoforms. The renal tubule is a major site of Klotho expression, and when kidney disease progresses, Klotho expression falls[4]. This decline reflects a loss of renal resilience and metabolic muscle, and a shift toward a pro-inflammatory, pro-fibrotic, and pro-calcific milieu[4,5]. In this sense, Klotho is not simply a marker of injury; it represents a window of opportunity which can be opened by exercise[6]

Physiology And Pathology

The most established biology of Klotho is its role in phosphate and mineral handling. In CKD, disordered phosphate metabolism a central driver of vascular calcification, secondary hyperparathyroidism, bone disease, and excess cardiovascular risk. Klotho participates in the FGF23 axis and helps regulate mineral balance. When Klotho is deficient, the system becomes maladaptive. FGF23 rises, phosphate handling deteriorates, and skeletal as well as vascular health worsen. Thus, CKD-mineral bone disorder is not merely a disorder of calcium, phosphate, and PTH, but a broader failure of endocrine coordination[1-3].

Klotho also intersects with oxidative stress, mitochondrial dysfunction, and cellular senescence. Experimental work suggests that Klotho exerts renoprotective effects through modulation of stress-response pathways and suppression of inflammatory injury[1-3]. This is especially relevant in diabetic kidney disease, where metabolic excess, glucotoxicity, lipotoxicity, and haemodynamic stress converge[7,8]. In such a setting, a molecule associated with renal protection naturally attracts attention (Table 1).

Beyond its role in mineral metabolism, Klotho has emerged as an important regulator of renal fibrosis, inflammation, and tissue repair[1-3]. Experimental studies demonstrate that Klotho suppresses transforming growth

Table 1: Biological functions, mechanisms and clinical implications of Klotho in kidney health and disease

Biological role	Major mechanism	Clinical implication	Potential therapeutic relevance
Mineral metabolism	Co-receptor for FGF23; regulates phosphate excretion and vitamin D metabolism	Prevents hyperphosphataemia and CKD-MBD	Target for CKD-MBD management
Renal ageing	Anti-senescence protein	Delays renal ageing and nephron loss	Biomarker of biological kidney age
Oxidative stress	Enhances antioxidant defence; suppresses ROS generation	Protects tubular cells	Reduces progression of CKD
Inflammation	Inhibits NF-κB signalling and inflammatory cytokines	Decreases chronic renal inflammation	Potential anti-inflammatory therapy
Fibrosis	Suppresses TGF-β and Wnt/β-catenin pathways	Reduces renal fibrosis	Anti-fibrotic therapeutic target
Vascular calcification	Improves phosphate handling and inhibits vascular smooth muscle osteogenic transformation	Reduces cardiovascular disease	Cardiorenal protection
Endothelial function	Preserves nitric oxide bioavailability	Improves vascular health	Reduces endothelial dysfunction
Mitochondrial function	Preserves mitochondrial integrity and ATP production	Improves cellular energy metabolism	Protects against ischemic injury
Cellular apoptosis	Limits apoptosis and promotes cell survival	Enhances tubular repair	Improves recovery after AKI
Insulin signalling	Modulates insulin/IGF-1 pathway	Links kidney to metabolic health	Important in diabetic kidney disease
Immune regulation	Modulates innate immune responses	Reduces chronic inflammation	Emerging immunomodulatory target
Exercise responsiveness	Exercise increases circulating Klotho	Explains systemic benefits of physical activity	Supports exercise prescription in CKD

AKI- acute kidney injury; ATP- adenosine triphosphate; CKD- chronic kidney disease; CKD-MBD- chronic kidney disease-mineral and bone disorder; FGF23- fibroblast growth factor 23; IGF-1- insulin-like growth factor-1; NF-κB- nuclear factor-kappa B; PTH- parathyroid hormone; RAAS- renin-angiotensin–aldosterone system; ROS- reactive oxygen species; TGF-β- transforming growth factor-beta; Wnt- Wingless/Integrated signaling pathway.

Table-2: Factors influencing circulating Klotho levels.

Increase Klotho	Decrease Klotho
Regular aerobic exercise	Chronic kidney disease
Weight reduction	Diabetes mellitus
RAAS blockade	Ageing
SGLT2 inhibitors	Hyperphosphataemia
Vitamin D receptor activation	Smoking
Healthy diet	Chronic inflammation
Blood pressure control	Oxidative stress
Good glycaemic control	Acute kidney injury
Physical fitness	Renal fibrosis
Healthy sleep	Uremia

CKD- chronic kidney disease; nsMRA- non-steroidal mineralocorticoid receptor antagonist; RAAS- renin-angiotensin-aldosterone system; SGLT2- sodium-glucose cotransporter-2..

factor-β (TGF-β) signalling, inhibits epithelial-to-mesenchymal transition, reduces extracellular matrix deposition, and attenuates renal fibrosis[9,10]. Klotho also modulates Wnt/β-catenin, NF-κB, and insulin/IGF-1 signalling pathways, thereby reducing oxidative stress and cellular senescence[10]. These pleiotropic actions position Klotho as a master regulator of renal resilience rather than simply a biomarker of kidney injury. Consequently, declining Klotho levels may represent one of the earliest manifestations of biological kidney ageing, preceding measurable reductions in glomerular filtration rate[2,3].

Opportunity

Several therapeutic approaches aimed at restoring Klotho activity are currently under investigation. These include recombinant soluble Klotho protein, gene therapy, epigenetic modulation, stem-cell based therapies, vitamin D receptor activation, renin-angiotensin system blockade, sodium-glucose cotransporter-2 inhibitors, mineralocorticoid receptor antagonists, and lifestyle interventions such as regular aerobic exercise[11,12]. Although none has yet entered routine clinical practice as a dedicated Klotho therapy, many contemporary nephroprotective interventions may exert part of their beneficial effects through preservation or enhancement of endogenous Klotho expression.

Klotho currently belongs more to the realm of pathobiology than routine practice. We do not yet measure it to guide therapy in ordinary clinical care, nor do we have established Klotho-targeted drugs in standard nephrology armamentarium. In fact, the best intervention to increase klotho is exercise[6]. Beyond exercise, several pharmacological and lifestyle interventions may influence endogenous Klotho expression (Table 2), although definitive Klotho-directed therapies remain under development.

What makes Klotho especially relevant now is its integration with the broader field of metabolic medicine. CKD is increasingly understood not only as a renal condition, but as a systemic metabolic syndrome[13]. Patients present with multiple complaints, complications and comorbidities. Klotho offers a unifying narrative for this complexity. It links the kidney to the bone, the vasculature, the myocardium, and the pancreas. It also fits neatly into the emerging language of cardiorenal-metabolic risk, where the boundaries between specialties are less useful than the pathways that connect them.

The Way Forward

Klotho is a reminder we still do not understand all the secrets of the kidney. The kidney has a central role in determining the status of health and disease. We now have drugs that can slow the decline of kidney function. The future of nephrology will likely belong to therapies that do more than slow decline; they will restore biologic reserve. As nephrology evolves from a discipline focussed on filtration to one centered on preservation of renal resilience, Klotho may emerge as both a biomarker and therapeutic target that bridges kidney, cardiovascular, skeletal, and metabolic health.

Klotho-centred diagnostics and therapeutics may help modulate senescence, enhance renal resilience, and improve metabolic and endocrine health. In that sense, Klotho represents hope for a healthier future. Till then, we need to exercise.

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