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Min Review

Beyond the Kidney-Klotho and the Cardiovascular System

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Introduction

Klotho is a pleiotropic protein that functions by modulating oxidative stress, inflammation, and calcium-phosphate metabolism, playing an integral kidney health as well as aging and disease prevention. The crucial roles in various metabolic pathways, that Klotho is involved in have been inextricably linked to chronic kidney disease (CKD). Given the link between mortality in CKD to cardiovascular disease, it is highly plausible that Klotho also exerts influence the development and prevention of cardiovascular diseases. Klotho is involved in the reduction of lipid peroxidation and inflammation while protecting against endothelial damage and vascular calcification. Additionally, Klotho enhances vascular flexibility and inhibits the progression of cardiac fibrosis. The cardioprotective effects of Klotho stem from interactions with diverse receptors and ion channels. As a pleiotropic protein, Klotho represents a promising target for therapeutic strategies aimed at treating cardiovascular diseas es. This review explores the cardiotoxic and cardioprotective links between the cardiovascular system and Klotho and explores pharmaceutical strategies that leverage Klotho cardiometabolic effects for potential future research directions.

Klotho Background

The 1997 study by *Kuro-o, et al.* on a mutant mouse exhibiting age-related degeneration across multiple organs led to the discovery of the Klotho gene and its classification within a family of single-pass transmembrane proteins, including *α*-, *β*-, and *Y*-Klotho isoforms. Klotho functions both as a membrane-bound co-receptor and a soluble circulating factor, playing key roles in endocrine regulation, cellular signaling, and oxidative stress modulation. The soluble form arises from the cleavage of membrane-bound Klotho and acts as a systemic hormone, while the membrane-bound form serves as a co-receptor for fibroblast growth factor 23 (FGF23), crucial for phosphate and vitamin D metabolism. Specifically, *α*-Klotho,

commonly referred to as Klotho, facilitates the high-affinity binding of FGF23 to its receptor FGFR1, forming the physiological receptor complex necessary for FGF23 activity. Klotho does not penetrate the blood-brain barrier, and the exchange of this protein between the interstitial fluid of the brain and CSF is normally virtually absent. Thus, the presence of three "pools" of Klotho is assumed: cerebral Klotho (Klotho of the brain tissue), CSF Klotho, produced by the choroid plexus, and serum Klotho synthesized by the kidneys. The existence of these independent pools is indicated by the absence of correlations between the serum and CSF Klotho in normal conditions [1]. Primarily expressed in the renal proximal and distal tubules, Klotho is essential for maintaining phosphate and mineral homeostasis by enabling FGF23 to regulate phosphate reabsorption and vitamin D synthesis. This FGF23–Klotho axis prevents hyperphosphatemia and its complications, such as vascular calcification. Additionally, Klotho exerts anti-aging effects by mitigating oxidative stress, inflammation, and cellular senescence, contributing to systemic homeostasis and longevity [2].

Cardiovascular Effects of Klotho

The considerable attention in Klotho emerged from the inverse correlation with aging, extending to its broad age-related effects on various systems. Klotho in circulation is recognized as having the enzyme activity of autocrine, endocrine and paracrine hormone, playing roles in the regulation of nitric oxide in vascular endothelial cells and in calcium homeostasis [3]. Previous clinical study demonstrated that potential link between Klotho deficiency and enhanced oxidative stress in patients with kidney disease. Klotho is often found at reduced levels in patients with coronary microvascular disease, even in the absence of obstructive coronary artery disease, a hallmark of early coronary artery aging. Elevated Klotho levels have been linked to an increase in circulating endothelial progenitor cells expressing vasculoprotective markers. The link between the regulation of phosphate and calcium homeostasis, purported exerts profound influence on vascular calcification, thereby connecting renal and cardiovascular diseases [4]. Although the vasculature does not express Klotho and attributing arterial calcification as a direct consequence of Klotho deficiency is complicated by multiple confounding factors, this protein may serve as a valuable therapeutic target for early cardiovascular diseases.

Cardiovascular Disease

Using US NHANES data, Yang and colleagues evaluated the optimal cutoff value of serum α-klotho for predicting all-cause mortality risk in the general population(n=13,746) mean age of 56.19 ± 10.42 years old, identifying 603.5 pg/ml. Individuals with serum α-klotho <603.5 pg/ml) had a significantly higher risk of all-cause and cardiovascular mortality, showing low serum α-klotho level was an independent risk factor for all-cause and cardiovascular mortality in people with cardiovascular disease related comorbidities and/or renal insufficiency. A low serum α-klotho concentration (<603.5 pg/ml) could serve as a marker of all-cause and cardiovascular mortality [5].

Another analysis of NHANES (2007-2014) among participants with hypertension (n=6,778) reported 36,714 person-years of follow-up, with 575 documented deaths and lower serum Klotho concentration was associated with increased all-cause mortality, but not cardiovascular mortality after multivariate adjustment [6]. A threshold value of 574 pg/mL was identified, such that the hazard ratio was 0.79 for individuals with Kloth <574 pg/mL. Higher serum Klotho concentration was associated with lower all-cause mortality, but not cardiovascular mortality in patients with hypertension with or without chronic renal impairment.

Klotho and Left Ventricular Hypertrophy

In patients with and without CKD, enhanced circulating FGF23 levels associate with pathologic cardiac remodeling [7], i.e., left ventricular hypertrophy (LVH) and myocardial fibrosis and increased cardiovascular mortality. Interestingly, these mice remain protected from cardiac hypertrophy. Although experimental studies reveal that FGF23 induces hypertrophic growth of cardiac myocytes, independent of its co-receptor Klotho. Recent research also shows that FGF23 is produced within the heart and significantly upregulated in various clinical and experimental models of cardiac remodeling and heart failure, regardless of renal function status. At the cellular level, FGF23 is expressed not only in cardiac myocytes but also in cardiac fibroblasts, vascular smooth muscle cells, endothelial cells of coronary arteries, and inflammatory macrophages. Evidence suggests that FGF23 secreted by cardiac myocytes can activate pro-fibrotic signaling in myocytes, promoting fibrosis-related pathways in fibroblasts and ultimately contributing to cardiac fibrosis through a paracrine mechanism. Animal models with Klotho deficiency develop LVH and cardiac fibrosis. Conversely, restoring Klotho expression or administering recombinant Klotho in rodents has been shown to alleviate pathological cardiac remodeling and heart failure [8]. Furthermore, in transgenic mice overexpressing Klotho hypertension and elevated systemic FGF23 levels are observed, purportedly due to Klotho-induced stimulation of FGF23 production by bone.

Klotho and Heart Failure

The association between klotho and heart failure was evaluated using NHANES data (n=11 271) in Americans aged 40-80 years. Serum α-klotho was divided into four quartiles for analysis. Multivariate logistic regression analyses revealed a per-standard deviation increase in serum klotho level was associated with a decrease in prevalence of heart failure [odds ratio (OR): 0.76, 95% confidence interval (CI): 0.68-0.85). The ORs for participants in quartiles 2 to 4 were 0.77 (95% CI: 0.58-1.01), 0.70 (95% CI: 0.52-0.93) and 0.71 (95% CI: 0.53-0.95), respectively, compared with those in quartile 1, with significant sex and race differences.

A study to assess the changes in klotho and FGF-23 levels 1-month among 29 patients (median age ~68y, 79% male) after dapagliflozin in patients with stable heart failure and reduced ejection fraction (HFrEF) [9] among, as part of the double-blind, randomized clinical trial [DAPA-VO2 (NCT04197635)] was conducted.

Compared to placebo, patients on dapagliflozin showed a significant median increase of klotho as well as a decrease of FGF-23, albeit not significantly different from baseline.

The predictive value of Klotho specific CVDs was also analyzed in NHANES data from 2007 to 2016 (n=8,615) [10]. The lowest level of Klotho was significantly associated with CHF [odds ratio (OR)=1.46, 95% CI: 1.09-1.97] and MI (1.33, 1.02-1.74), but not CHD or stroke. Each unit increment in Klotho was positively associated with a 38 and 24% reduction in the prevalence of CHF and MI, respectively.

Serum levels of Klotho and FGF23 were measured in 287 patients with cardiomyopathy (CMP). Tissue samples from CMP (n=10) and healthy control hearts (n=10) were analyzed for Klotho mRNA and protein expression. Individuals in the first FGF23 tertile had a 4.1 times lower mortality, need for heart transplantation or assist device implantation compared to third tertile. Immunoblotting in tissue from 10 patients compared to 10 healthy controls confirmed upregulation of Klotho associated with increased expression of proteases [11] involved in cleavage of Klotho suggesting rather local effects of Klotho in the heart.

Klotho and Coronary Artery Disease (CAD)

Abdominal aortic calcification (AAC) has been recognized as an independent predictor of CVD incidence and mortality. *Wang, et al.* [12] investigated severe AAC in US civilians using 2013-2014 NHANES data (n=2267) from individuals aged 40-79 years. The association between Klotho and severe AAC revealed an odds ratio (OR) (95% CI) among those with AAC in klotho quartiles 2-4 of 0.83 (0.52, 1.32), 0.56 (0.34, 0.94), and 0.54 (0.32, 0.92), respectively, compared with those in quartile 1.

A two-sample Mendelian randomization (MR) study was designed, with 5 single-nucleotide polymorphisms associated with circulating α-Klotho levels utilized as instrumental variables [13]. MR)estimates on CVD outcomes derived from the fixed-effects inverse-variance weighted (IVW) approach by Sun and colleagues using different data sources suggested an inverse causal association of circulating Klotho concentrations with CAD [Odds ratio (OR), 0.97; 95% confidence interval (CI), 0.94, 1.00; P=0.044] and significant inverse association of circulating α-Klotho concentrations with AF (OR, 0.96; 95% CI, 0.93, 0.99; P=0.005), yet no causal association with HF.

Cardiopulmonary effects of Klotho

Klotho and Chronic Obstructive Pulmonary Disease (COPD)

(COPD) is accompanied by increased inflammation, persistent lung function decline, and extensive lung injury. The association among COPD adults and their klotho level was evaluated using data from the 2007 to 2012 NHANES (n=676), divided into COPD (n=403) and non-COPD (n=273) groups [14]. After stratification according to the levels of klotho, non-COPD individuals were shown to have higher klotho levels than those with COPD individuals with the risk of COPD gradually decreased with increasing α-klotho concentration < 1,500 pg./mL, while the risk of COPD increased as the α-klotho concentration increased to ≥1,500 pg./mL. Pulmonary ventilation function and the number of hemocytes differed among COPD patients also differed by klotho level.

In another NHANES analysis involving 4361 adults aged 40-79 years between 2013 and 2016 Klotho was negatively associated with COPD (OR=0.71) [15]. Meanwhile, compared with quartile 1, serum Klotho levels in quartiles 2-4 yielded odds ratios (ORs) (95% CI) for COPD were 0.84 (0.63~1.11), 0.76 (0.56~1.02), 0.84 (0.62~1.13), respectively. Serum Klotho was negatively associated with the incidence of COPD such that a 1unit increase was associated with a decreased risk of COPD by 29%.

The platelet to high-density lipoprotein cholesterol ratio (PHR) and prevalence of COPD [16], was also evaluated among NHANES participants 40 and 85 years in data from 1999-2018. Propensity score matching (PSM) showed that the odds ratio (OR) for PHR to predict COPD was 1.002. Restricted cubic spline analysis demonstrated a linear association between PHR and COPD prevalence both before and after PSM. Significant association between PHR and COPD prevalence was observed only in participants without hypertension. Receiver-operating characteristic curves showed significantly higher area under the curve for distinguishing COPD from non-COPD by PHR than platelet count and high-density lipoprotein cholesterol.

Cardiometabolic Effects of Klotho

In the context of metabolic disorders, Klotho helps mitigate chronic inflammation and oxidative stress, both of which play central roles in insulin resistance and cardiovascular complications. Lower Klotho levels are associated with the activation of pro-inflammatory pathways, such as NF-κB signaling, contributing to the systemic inflammation characteristic of metabolic syndrome. Additionally, Klotho supports adipose tissue health by promoting proper adipogenesis and minimizing ectopic fat accumulation, a key factor in metabolic dysfunction. Therapeutic approaches aimed at increasing Klotho expression or replicating its effects are being investigated as potential treatments for metabolic disorders, offering a promising strategy to address insulin resistance, dyslipidemia, and cardiovascular risk.

Klotho and Wnt- *β-catenin*

Plausibly, cardioprotective effects result from the ability of Klotho to inhibit or limit pathways involving insulin-like growth factor 1 (IGF-1), angiotensin II, WNT-β-catenin, PI3K, AKT, and reactive oxygen species (ROS) production in the heart. For example, Klotho blocks insulin/IGF-1 receptor activation. This blockage prevents downstream signaling inhibiting phosphorylation of insulin receptor substrates (IRS) and PI3K/Akt/mTOR signaling (*Zhao Y, et al*., 2015). The insulin/IGF-1 pathway connects with antioxidant mechanisms through the FoxO forkhead transcription factors (FOXOs). Blockade of insulin/IGF-1 pathways releases inhibition of the FOXOs, resulting in their nuclear migration and the expression of several genes encoding antioxidant enzymes, such as manganese

superoxide dismutase. Klotho blocks Wnt activation by binding to several Wnt ligands. In Klotho-deficient mice, excess Wnt activation promotes cell senescence, and has a negative impact on stem cell survival.

In patients with type 2 cardiorenal syndrome, Zhao and colleagues [17] investigated the role of Wnt signaling in heart and kidney injury in a mouse model of cardiac hypertrophy and heart failure induced by transverse aortic constriction (TAC). Eight weeks after TAC, cardiac function was impaired as evidenced by cardiac hypertrophy, inflammation, and fibrosis. The cardiac lesions were accompanied by upregulation of multiple Wnt ligands and activation of β-catenin, as well as activation of the renin-angiotensin system (RAS). Proteinuria and kidney fibrosis, accompanied by klotho depletion and β-catenin activation in the kidney was also observed. Tumor necrosis factor (TNF)-α was inversely associated with klotho, and induced β-catenin activation identifying Wnt/β-catenin signaling as a common pathogenic mediator of heart and kidney injury in type 2 cardiorenal syndrome after TAC.

Klotho and Cardiac Aging

Cardiac aging as evidenced by decreased fractional shortening, ejection fraction, and cardiac output as well as heart size and weight, cardiomyocyte size, and cardiac fibrosis. Among 24-month old mice, circulating Klotho levels were dramatically decreased. The Klotho gene mutation (KL-/-) largely decreased serum klotho levels and impaired heart function, whereas exogenous administration of Klotho prevented HF, LVF, and remodeling in both old mice and KL (-/-) mice. The authors hypothesized Klotho deficiency suppressed GR (glutathione reductase) expression and activity in the heart via inhibition of transcription factor Nrf2 (nuclear factor-erythroid 2 p45-related factor 2). They also speculated that cardiac-specific overexpression of GR prevented excessive oxidative stress, apoptosis, and HF, suggesting Klotho as a promising therapeutic strategy for aging-associated cardiomyopathy and heart failure.

Li-Zhen, et al. [18] also hypothesized that klotho deficiency plays an essential role in cardiac ageing *in vivo* and demonstrated that supplementation with exogenous klotho protects against cardiomyocyte aging *in vitro*. They measured the lifespan of wild-type (WT) and klotho-hypomorphic mutant (KL-/-) mice and recorded the cardiac function of the mice through echocardiography. Genetic klotho deficiency was associated with decreased lifespan and cardiac function, impaired autophagic activity and increased apoptotic activity. Exogenous klotho attenuated cardiomyocyte aging and reversed changes in autophagic and apoptotic activity caused by D-gal.

Cardiac aging increases the risk of HF with preserved ejection fraction (HFpEF). In aged wild-type and heterozygous Klotho-deficient mice receiving daily injection of Klotho for 10 weeks, followed by a comprehensive assessment of heart function by echocardiography, intracardiac pressure catheter, exercise tolerance, and cardiac pathology *Daneshgar, et al.* [19] showed that klotho deficiency accentuated cardiac hypertrophy, diastolic dysfunction, and exercise intolerance. Klotho administration ameliorated cardiac abnormalities and improved cardiac capillary densities. They also found that decreased Klotho was associated with Sirt1 deficiency. Klotho deficiency significantly increased hyperacetylation of several crucial cardiac contractile proteins, potentially impairing ventricular relaxation and diastolic function, thus predisposing to HFpEF. Conversely, Klotho administration restored Sirt1 expression in aged hearts and mitigated the DNA damage response pathway activation attenuating age-dependent DNA damage and cardiac diastolic dysfunction.

Klotho also facilitates the binding of FGF23 to receptors and plays a role, in the activation of the pro-hypertrophic calcineurin–NFAT pathway in the heart, such that the presence of soluble Klotho inhibits calcineurin–NFAT signaling. Moreover, the Klotho-induced alterations in FGF23-induced FGF receptor signaling may mitigate cardiac toxicity of FGF23, although the association between FGF23, atherosclerosis and arterial calcification is highly variable. Activation of the cardiac RAS–MAPK pathway by Klotho may also be involved in inhibiting apoptosis and enhancing cardiomyocyte survival.

In addition, a direct link between Klothos and inhibition of NF-κB and TGF-β as it relates to inflammation and fibrosis has been reported. Klotho prevents nuclear translocation of NF-κB, which is an essential step in the activation pathway. Collectively, Klotho is involved the inhibition of the NLRP3 inflammasome, and a reduction in endoplasmic reticulum (ER) stress, reactive oxygen species (ROS) and tissue fibrosis. This is of major interest because Klotho levels can be enhanced clinically, and there is the possibility of therapeutic intervention.

Klotho and Diabetes

As a key contributor to the pathogenesis of CVD, relationship between serum Klotho and diabetes warrants investigation. XX and colleagues analyzed the NHANES data (n=13751) from subjects aged 40-79 years. Interquartile analysis revealed as compared with quartile 1, serum Klotho levels in quartiles 2-4 yielded odds ratios (OR) (95% CI) of diabetes of 0.96 (0.80-1.15), 0.98 (0.82-1.18), and 1.25 (1.04-1.50), respectively., suggesting increased risk of diabetes. The RCS plot showed a U-shaped relationship linking serum Klotho levels with diabetes.

Therapeutic Potential of Klotho

Given the reported benefits of Klotho in combating aging and various diseases in preclinical models there is significant interest in exploring its potential applications in humans. In humans, it is well-established that plasma Klotho levels decline with age and in common conditions like chronic kidney disease, diabetes, and cardiovascular disorders. As a result, restoring normal Klotho levels appears to be a promising and safe therapeutic goal. Several drugs have already been identified for their potential to elevate Klotho in specific diseases. Many studies have primarily focused on raising Klotho levels to normal or near-normal levels rather than exceeding them. Research in mice suggests that Klotho overexpression might extend lifespan, though safety concerns remain, as factors

such as insulin resistance could become relevant. It is important to note that most of the available data on Klotho-based treatments comes from rodent studies.

Producing and using Klotho as a therapeutic agent is both technically challenging and expensive due to its nature as a membrane-bound protein. Additionally, elevated serum Klotho levels can disrupt calcium and phosphate balance, potentially causing conditions like hypocalcemia and hypophosphatemia. However, studies have shown that targeting the KL1 domain alone can induce protective effects without altering phosphate levels. This led European Wellness (EW) to propose that small peptides derived from Klotho could replicate its therapeutic effects while minimizing side effects.

In a mouse model, recombinant Klotho reduced hyperphosphatemia and eventually rescued the CKD-associated VC. Also, CKD mice in this experimental model demonstrated a less severe VC than wild-type CKD mice [20].

The mechanism of its protective role is that Klotho has anti-oxidative and anti-apoptotic effects in VSMCs to decease VC. Upregulation of Klotho gene significantly decreased superoxide production in VSMCs in protein level through inhibiting cAMP-PKA pathway (*Donate-Correa, et al*., 2023).

Even in case of the preserved renal functions, Klotho demonstrated relevant cardioprotective actions in patients after ST-elevation myocardial infarction. Such patients showed that Klotho treatment prevented reduction in ejection fraction and MI-related ECG changes, including prolonged QRS, JT, QTc, and TpeakTend intervals and premature ventricular contractions after MI. Klotho prevented increased diastolic Ca2+ leak by blocking activation of the Ca2+/calmodulin-dependent kinase type II (CaMKII) pathway, preventing hyperphosphorylation. Finally, Klotho supplementation protected against functional and structural cardiac remodeling and ameliorated ventricular arrhythmic events by preventing intra cardiomyocyte Ca2+ mishandling [21].

Peptides act as signaling molecules that bind to receptors on cells, initiating processes like migration, proliferation, and differentiation, with these effects depending on the peptide sequence. When used in scaffolds, peptides enhance stem cell adhesion and support tissue regeneration. Stem cell-derived peptides, short protein fragments from or synthesized by stem cells, mimic the functions of native stem cell proteins and show promise in regenerative medicine by facilitating tissue repair. These peptides, derived from various stem cells, including mesenchymal stem cells (MSCs), accelerate wound healing and may offer therapeutic benefits for inflammatory conditions due to their anti-inflammatory properties. Peptides that emulate extracellular matrix (ECM) components also improve cell adhesion and migration.

The structure and function of cells influence the production of biologically active substances, such as peptides. By leveraging organ- and tissue-specificity, peptide therapies can rejuvenate cellular signaling, promoting peptide synthesis or restoring normal signaling pathways, which helps in tissue regeneration. Peptides' short length and low molecular weight make them ideal for efficient large-scale synthesis, extraction, and distribution for therapeutic use.

Nano Organo Peptides (NOPs) and Mito Organelles (MO) peptides are widely used in humans and animals. NOPs, small peptides about 3 nm in size and under 10 kDa, are derived from mammalian stem cells using a specialized filtration process. This process isolates substances under 10 kDa, ensuring specificity. Their small size and solubility allow for sublingual or injectable administration, and they have been explored for use in cosmetics and organ regeneration. In contrast, MO peptides, derived from mitochondria-specific components, aim to enhance mitochondrial function. Mitochondrial dysfunction contributes to cellular decline, including apoptosis, and MO peptides help restore mitochondrial activity, promoting regeneration. These peptides are larger and specifically designed for mitochondrial rejuvenation.

Mitochondria are essential for energy production in cells, and their dysfunction is often detected early in diseases affecting the kidney, heart, and brain. Mitophagy, the process of mitochondrial autophagy, serves as a sensitive test for age-related dysfunction. Mitochondrial dysfunction can lead to reactive oxygen species (ROS) activation, peptide malfunction, cell damage, and apoptosis. Given that mitochondria produce a small number of peptides and polypeptides encoded by mitochondrial DNA (mtDNA), maintaining healthy mitochondria is crucial for cellular function. Mitochondrial RNA provides information on organ-specific peptides secreted by various cells, including cardiomyocytes and fibroblasts.

Peptides can also mimic growth factor activity, supporting cell proliferation and differentiation. EW is investigating the potential of stem cell-derived peptides in treating type 1 diabetes (T1D), where they could replicate the function of insulin-producing beta cells, regulate blood sugar, and protect beta cells from immune damage. Given the link between T1D and chronic kidney disease (CKD), Klotho peptides are a promising area of research. EW and the BioPep Research Group have evaluated peptide therapies, such as NOP and MO peptides, developed using a proprietary extraction process. In a study on NOD mice, intramuscular administration of MO peptides derived from thymus and pancreatic extracts helped delay or prevent beta-cell destruction in pancreatic islets. Cytokine analysis showed significant differences in erythropoietin (EPO) and chemokine ligand 5 (CCL5/RANTES) levels between the MO-treated and control groups. MO peptide-treated mice had higher EPO and CCL5 concentrations, providing preliminary evidence that MO peptides may delay T1D onset and warrant further investigation as a therapeutic approach. Notably, these pathways are involved in the inflammatory cascade observed in uremic inflammation.

Summarizing, Klotho protein is a promising therapeutic molecule for CKD-induced VC. Maintenance or external injections of Klotho could improve VC in CKD. Such clinical findings need to be proven in future research.

In conclusion, Klotho-derived peptides hold significant promise for regenerative medicine by mimicking natural biological functions. NOPs and MO peptides expand therapeutic possibilities by targeting tissue-specific and mitochondrial functions, promoting cellular rejuvenation, and restoring organ vitality. These peptides, including MO peptides' ability to delay beta-cell destruction in diabetes and Klotho peptides' anti-aging effects, represent a convergence of regenerative and protective strategies, offering a transformative approach to treating aging, diabetes, and degenerative diseases through targeted repair and revitalization.

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