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## THE IMPORTANCE OF KLOTHO PROTEIN IN THE DIAGNOSIS OF CHRONIC KIDNEY DISEASE

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**Abstract:** Chronic kidney disease (CKD) is an intrinsically systemic infection that alludes to a long-term misfortune of kidney work. The movement of CKD has repercussions for other organs, driving to numerous sorts of extrarenal complications. Seriously ponders are presently being attempted to uncover the hazard components and pathophysiological component of this malady. Amid the past 20 a long time, expanding prove from clinical and fundamental ponders has shown that klotho, which was at first known as an anti-aging quality and is primarily communicated within the kidney, is altogether connected with the improvement and movement of CKD and its complications. Here, we talk about in detail the part and pathophysiological suggestions of klotho in particle clutters, the aggravation reaction, vascular calcification, mineral bone clutters, and renal fibrosis in CKD. Based on the pathogenic component of klotho insufficiency and klotho decrease in pee early in CKD organize 2 and indeed prior in CKD stage 1, it isn't troublesome to get it that solvent klotho can serve as an early and delicate marker of CKD. Besides, the anticipation of klotho decay by a few components can weaken renal wounds, impede CKD movement, enhance extrarenal complications, and make strides renal work. In this audit, we center on the capacities and pathophysiological suggestions of klotho in CKD and its extrarenal complications as well as its potential applications as a demonstrative and/or prognostic biomarker for CKD and as a novel treatment methodology to progress and diminish the burden of comorbidity in CKD.

**Key words:** Chronic kidney disease, klotho protein, pathogenic mechanism, prognostic biomarker.

## INTRODUCTION

Chronic kidney disease (CKD) could be a dynamic systemic illness that irreversibly changes the work and structure of the

kidney, over months or a long time. CKD movement has repercussions for other organs, applying numerous negative

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systemic impacts on various organs, counting those of the cardiovascular framework, driving to cardiovascular infections, which increase the chance of mortality [1]. Within the past 3 decades, seriously considers in creatures and people have been performed to uncover the chance variables and pathophysiological component of this infection. These ponders have set up that the initial malady prepare causes a beginning misfortune of nephron unit; at that point, renal illnesses advance to renal disappointment as a result of useful adjustments mediating within the kidney, driving to damage in other organs. In addition, numerous components are included in this handle, counting an assortment of cytokines, development variables and vasoactive substances. As of late, more confirmations have recommended that the advancement and movement of CKD are essentially related with a decline in klotho, which was at first depicted as an anti-aging quality [2].

The klotho quality is mainly expressed within the cell surface film of proximal and distal renal tubules. Under typical physiological conditions, the kidney could be a major controller that makes a difference keep up klotho levels. However, in people and in creature models with CKD, klotho levels decrease and are went with by renal lacking. Tentatively, klotho-deficient mice and CKD subjects have comparative phenotypes, proposing that klotho is firmly related with the pathogenic component of CKD. Moreover, assist prove has appeared that klotho is not only an early biomarker of CKD, but too a potential helpful target for CKD [3]. Hence, based on the relationship between klotho and CKD, we here methodically review the capacities, physiopathological characteristics, and potential applications of klotho within the related signs and complications of CKD.

Klotho family individuals incorporate  $\alpha$ -,  $\beta$ -, and  $\gamma$ -klotho qualities based on their anticipated essential arrangements.  $\beta$ - and  $\gamma$ -klotho were found based on their homology with  $\alpha$ -klotho, and they all share a single-pass transmembrane protein.  $\beta$ -Klotho is transcendentally communicated within the liver but is additionally found within the kidney, intestine, and spleen and intervenes the movement of individuals of the fibroblast development calculate (FGF) family, such as FGF-19 and -21.  $\gamma$ -Klotho is communicated within the kidney and skin and has undefined capacities [4]. In this survey, we as it were center on  $\alpha$ -klotho; the term klotho within the tAcute kidney injuryng after passages alludes to  $\alpha$ -klotho.

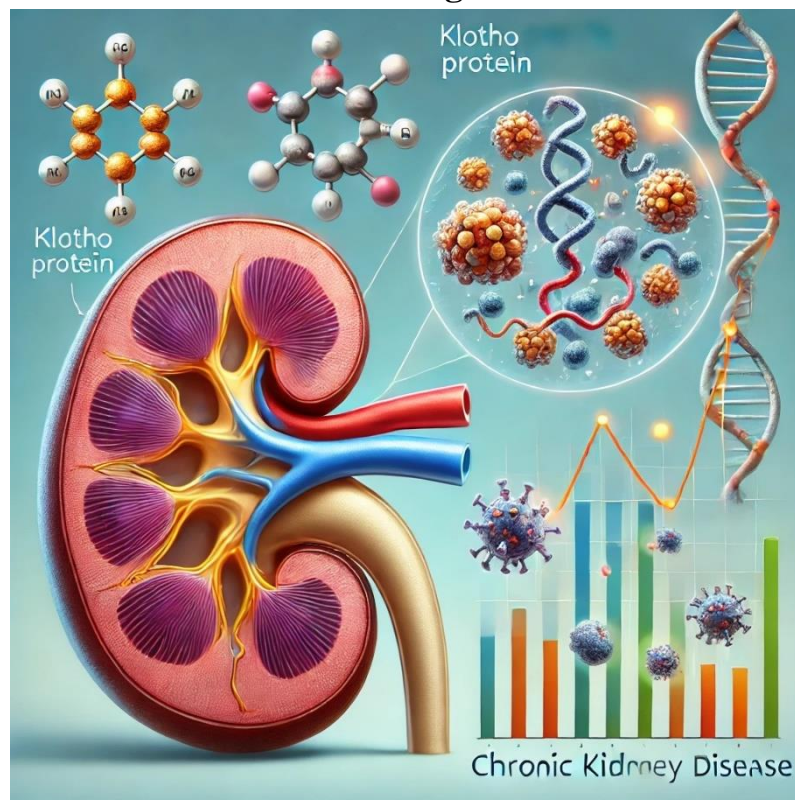
$\alpha$ -Klotho is composed of five exons that compare 1,012 amino acids within the human protein and 1,014 amino acids within the mouse protein (Fig. 1). The protein comprises of a huge extracellular space, counting 980 N-terminal buildups taken after by a 21-amino-acid transmembrane space and a little space of 11 buildups comparing to the intracellular C-terminus. The extracellular space of film klotho comprises of two rehash groupings of 440 amino acids named Kl1 and Kl2, which are created by full-length transcript joining and can be cleaved by the metalloproteinases ADAM-10 and ADAM-17 and discharged into circulation as dissolvable klotho (cleaved klotho) [5]. In expansion, an on the other hand joined klotho mRNA transcript has been hypothesized to code for an emitted klotho protein, which would liken to the Kl1 space, but this putative protein has not been recognized and has not been recognized in human serum hence distant; it has been watched as it were in in vitro frameworks. Besides, a later consider appeared that this elective klotho mRNA was corrupted by nonsense-mediated mRNA rot (NMD), at last coming about in no active protein

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interpretation. Soluble klotho is the most useful frame within the circulation [6] and is identified within the blood, pee, and cerebrospinal fluid, applying its work by

acting as a hormone. Moreover, another utilitarian shape of klotho happens, named membrane-bound klotho, which is basically included in FGF receptor flagging.

**Fig. 1**



The structure of the klotho quality and protein. a The structure of the klotho qualities from people and mice. b The structure of the klotho protein. Solvent klotho proteins are created by full-length transcript joining at the shown  $\alpha$  and  $\beta$  cut destinations, comprising the whole extracellular space, or at the single Kl1 or Kl2 spaces.

The work and pathophysiological suggestions of klotho in CKD

FGF23 has a place to the FGF family. Numerous considers have appeared that FGF23 not as it were increments the urinary excretion of phosphate but moreover in a roundabout way stifles intestinal phosphate assimilation by down-regulating the

generation of  $1\alpha,25$ -dihydroxyvitamin D3 ( $1\alpha,25$ -dihydroxyvitamin D3. FGF23 transduces signals by authoritative to its receptors to phosphorylate downstream flagging atoms [6]. There are four distinctive FGF receptors (FGFRs), FGFR1-4; these proteins are tyrosine kinase receptors and have tall or moo liking for FGFs. Since of their need of a heparan sulfate-binding space, FGF23 requires full-length klotho to change over the canonical FGFR into a particular high-affinity receptor to operate in target tissues [7]. As of late, research has appeared that within the complex comprising of the shed extracellular space of klotho, the FGFR1c ligand-binding space, and FGF23, klotho at the same time ties FGFR1c by its D3 space and FGF23 by its C-

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terminal tail, in this way coming about in FGF23-FGFR1c vicinity and conferring soundness [8]. In this way, klotho is a basic co-receptor for the authoritative of FGF23 to its receptors.

In proximal renal tubules, blood-borne FGF23 ties to FGFR-klotho complexes and specifically actuates extracellular signal-regulated kinase (extracellular signal-regulated kinase)1/2 and serum/glucocorticoid-regulated kinase (SGK)-1 signals. In this way, SGK-1 phosphorylates the Na<sup>+</sup>/H<sup>+</sup> trade administrative cofactor (NHERF)-1 to down-regulate layer expression of the key sodium phosphate cotransporter NaPi-2a, in this way driving to an increment in urinary phosphate excretion [9]. Misfortune of membrane-bound klotho expression limits FGF23-stimulated flag transduction through FGFR-klotho complexes. It has been appeared that a particular cancellation of klotho in proximal renal tubules was incapable to extend renal phosphate excretion in vivo [10], proposing that the impact of FGF23 on phosphate excretion is restricted by proximal tubular klotho insufficiency. Moreover, FGF23 smothers renal 1 $\alpha$ -hydroxylase expression, which is the key chemical dependable for 1 $\alpha$ ,25-dihydroxyvitamin D3 generation, by a klotho-dependent flagging instrument in proximal renal tubules [11]. In expansion, solvent klotho directly regulates phosphorus excretion within the kidney and partakes in systemic mineral homeostasis by controlling 1 $\alpha$ -hydroxylase action and parathyroid hormone (PTH) and FGF23 discharge [12, 13]. These comes about propose that klotho lack limits its direction of FGF23 generation and hyperphosphataemia remains the foremost controller of FGF23 emission in CKD. The impact of FGF23 on both phosphate and 1 $\alpha$ ,25-dihydroxyvitamin D3 is included in FGFR1, FGFR3, and FGFR4, particularly

FGFR1. In expansion, it has been distinguished that as with the mineral parameters, FGF23 and phosphate are expanded, whereas klotho and 1 $\alpha$ ,25-dihydroxyvitamin D3 are diminished in CKD, particularly in early stages, but serum phosphate. These changes in mineral parameters play a central part within the pathophysiology of CKD. Notably, each unsettling influence within the mineral parameters can be pathogenic alone or can drive and overstate the unsettling influence of the other parameters [14].

It was already detailed that dissolvable klotho could be a controller of the epithelial calcium channel transient receptor potential vanilloid-5 (TRPV5), a glycoprotein that's fundamental for the section of calcium into calcium-transporting renal epithelial cells. TRPV5 direction by klotho is thought to function as takes after: solvent klotho particularly hydrolyses sugar buildups from the glycan chains on TRPV5, which in turn stabilizes TRPV5 within the film through interaction of the sugar buildups with extracellular galectin. In any case, the cellular discharge prepare of klotho is vague. As of late, a diminish in renal calcium reabsorption and a renal layer plenitude of TRPV5 were watched in klotho-knockout mice, comparative to the finding in FGF23-knockout mice, but klotho not one or the other co-localizes with TRPV5 nor is directed by FGF23. Based on these comes about, it can be propped that FGF23 capacities by official to FGFR-klotho complexes, in this way specifically balancing calcium reabsorption in distal renal tubules. In differentiate, hypocalcaemia (calcium lack) diminishes the circulating concentrations of FGF23. This diminish in FGF23 might be a reaction that dodges an ensuing reduction in calcitriol, which seem worsen hypocalcaemia. Due to calcium and sodium disregulation in renal infections, the novel



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interface between FGF23 and the digestion system of these particles may have major pathophysiological suggestions in CKD [15].

Recognizably, film receptors of solvent klotho have not already been distinguished. A later think about found that  $\alpha 2$ -3-sialyllactose, which is show within the glycan of monosialogangliosides, could be a receptor of dissolvable klotho. Dissolvable klotho ties to ganglioside-enriched lipid flatboats to control PI3K signalling. Besides, another thinks about recognized the key protein buildups within the K11 space that are likely included in authoritative to  $\alpha 2$ -3-sialyllactose, which down-regulates TRPC6 channels and secures against stress-induced cardiac hypertrophy. These comes about give modern knowledge that focusing on sialic acids may be a common component fundamental the pleiotropic activities of dissolvable klotho [16].

Irritation is multifactorial in CKD, and this infection is considered a prototypical illustration of incendiary malady and untimely maturing. There are numerous proinflammatory components expanded steadily in CKD as renal work falls flat, counting interleukin (IL)-6, serum fetuin-A, and tumor corruption calculate (TNF). Atomic calculate  $\kappa B$  (NF- $\kappa B$ ) controls numerous cellular forms, such as antiapoptotic reactions, oxidative push, and particularly, provocative reactions [17]. In typical circumstances, NF- $\kappa B$  is found within the cytoplasm in a dormant shape, connected to its inhibitory proteins, termed inhibitory  $\kappa B$  (I $\kappa B$ ). In reaction to different boosts, such as TNF, two serine buildups at positions 32 and 36 within the N-terminal locale of I $\kappa B$  are phosphorylated. This phosphorylation actuates I $\kappa B$  ubiquitination by the E3-I $\kappa B$  ubiquitin ligase complex, causing its corruption by the 26S proteasome, hence driving to NF- $\kappa B$  translocation to the core and the coordinate

enactment of downstream quality translation [23, 68]. More prominent NF- $\kappa B$  movement increments the expression of proinflammatory arbiters, such as cytokines and attachment atoms. A few thinks about have shown that NF- $\kappa B$  plays an urgent part within the movement of unremitting renal irritation, whereby the hindrance of NF- $\kappa B$  diminishes the levels of a few proinflammatory cytokines and renal harm.

One ponder has appeared that there's a bidirectional relationship between klotho and NF- $\kappa B$  [23]. On the one hand, klotho expression is down-regulated by an NF- $\kappa B$ -dependent mechanism. Reduced klotho within the blood and pee has been watched in human CKD. In a nephrotoxic intense kidney harm mouse show, klotho expression was too diminished, and blockage of TNF-related weak inducer of apoptosis (Change), which may be a part of the TNF superfamily, was able to return kidney klotho levels and protect renal work. Additionally, the hindrance of NF- $\kappa B$  anticipates TWEAK-mediated diminishes in klotho levels [74]. In this way, proinflammatory cytokines, such as TWEAK, negatively direct the expression of klotho through an NF- $\kappa B$ -dependent component, and NF- $\kappa B$  may be a key donor to the direction of klotho expression.

On the other hand, klotho is an anti-inflammatory modulator that adversely controlled NF- $\kappa B$ , subsequently driving to a diminish in proinflammatory quality transduction. It has been detailed that TNF increments vascular cell grip protein 1 (VCAM-1) and intercellular attachment atom 1 (ICAM-1) expressions in endothelial cells, whereas klotho can smother TNF-induced increments in ICAM-1 and VCAM-1 expression by weakening NF- $\kappa B$  movement. Besides, in klotho-mutated mice, the exogenous expansion of dissolvable klotho or the overexpression of membranous

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klotho in tissue culture smothers NF- $\kappa$ B actuation and NF- $\kappa$ B-mediated provocative cytokines by means of an instrument that includes the phosphorylation of serine (536) within the transactivation space of RelA. So also, an abundance of klotho restrains the PDLIM2/NF- $\kappa$ B pathway to diminish the generation of TNF- $\alpha$ , IL-6, and IL-12, and to improve cyclosporine A-induced nephropathy in vivo and in vitro [18]. In expansion, klotho can stifle NADPH oxidase 2 (Nox2) protein expression and weaken oxidative stretch in rodent aortic smooth muscle cells and can moreover stifle retinoic acid-inducible Gene-I (RIG-I)-mediated aggravation. In this way, klotho may act as an anti-inflammatory modulator within the kidney.

Vascular calcification (VC) shows up early within the course of CKD but gets to be much more predominant as kidney work falls apart, making a solid hazard of cardiovascular mortality and dreariness in patients with CKD and end-stage renal disease. VC can be classified based on the vascular location of unusual mineral statement, counting intimal calcification, average calcification, and valvular calcification, which are all exceedingly predominant within the CKD populace. It is presently clear that VC may be a cell-regulated obsessive prepare that includes numerous inhibitors and inducers. Beneath typical conditions, a few inhibitors ensure against VC by calcium and phosphate supersaturation, such as pyrophosphate, network Gla protein, and fetuin-A. Within the CKD populace, the entire work between inhibitors and inducers is unbalance, driving to the event of VC within the vessel dividers and valves. There are numerous inducers of VC in CKD, counting hypercalcaemia, provocative cytokines, and particularly, phosphate. Clinical prove appeared that the upregulation of serum phosphate is one of

numerous hazard components for VC within the CKD populace. Additionally, a developing sum of exploratory inquire about has uncovered the instrument of phosphate-induced VC, appearing that PiT-1 which is phosphate cotransporter in vascular smooth muscle cells (SMCs), is included in pathogenesis and promotes VC by acceptance of SMCs osteochondrogenic change and apoptosis and by direction of extracellular vesicles discharge and solidness [19]. These comes about recommend that hoisted phosphate could be a primary inducer of VC.

The expression level of klotho diminishes in patients with CKD and creature models, and is went with by renal disarranges [20]. It has been detailed that klotho lack causes tall circulating levels of Phosphate and VC event in mice with CKD. On the other hand, overexpression of klotho can improve phosphaturia, make strides renal work, and create much less calcification in vivo as well as stifle the sodium-dependent take-up of Phosphate and Phosphate-induced calcification of rodent vascular SMCs. Zhang et al. detailed that cleaved klotho protein constricts the Phosphate-induced human bone marrow mesenchymal stem cells separation into osteoblast-like cells in vitro through inactivation of the FGFR1/Extracellular signal-regulated kinase flagging pathway. In expansion, the up-regulation of klotho expression by the hindrance of rapamycin flagging too enhances VC and secures against vascular illness in CKD [20]. Another ponder appeared that Intermedin 1-53 weakens VC in rats with CKD by up-regulating membrane-bound klotho expression within the vessel divider. Later thinks about have affirmed that the steady conveyance of solvent klotho can decrease persistent hyperphosphataemia and VC in vitro and in vivo, and actuating peroxisome proliferator-activated receptor  $\gamma$  upgraded

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the expression of klotho to repress Phosphate-induced VC in vascular SMCs. These comes about proposed that klotho insufficiency is closely related with hyperphosphataemia and VC which upgrading klotho action plays a defensive part in hyperphosphataemia and VC in CKD.

CKD-mineral bone clutter (MBD) may be a recently named systemic clutter that starts early in organize 2 of CKD and is characterized by unusual serum biochemistries counting hyperphosphataemia and hypercalacemia, bone disarranges, and VC. The causes of VC and cardiovascular mortality related with CKD are incompletely ascribed to CKD-MBD. Later considers illustrate that components that are involved in renal damage and repair which are discharged into the circulation contribute to the pathogenesis of CKD-MBD; such components incorporate the Wnt flag inhibitors, Dickkopf 1 and sclerostin, as well as activin A and ActRIIA. The pathogenic components of the components of CKD-MBD incorporate VC, misfortune of renal klotho, hyperphosphataemia, osteodystrophy, vitamin D lack, expanded FGF23, cardiovascular illness, and hyperparathyroidism. In this survey, we basically center on the viewpoints related to klotho. As depicted already, the expression of klotho is essentially diminished in CKD. It has been detailed that this diminish in klotho is somewhat related to activin and ActRIIA flagging. Besides, the actuation of ActRIIA flagging by employing a ligand trap for the receptor essentially fortifies klotho levels. The coming about lessening in klotho limits its direction of FGF23 generation and clears out hyperphosphataemia as the principal controller of FGF23 emission in CKD. As of late, analysts have distinguished that klotho misfortune may be a key occasion within the renal and bone wounds in CKD-MBD mice, and endogenous klotho rebuilding by histone deacetylase

hindrance constricts CKD-associated bone complications in a mouse demonstrate of CKD-MBD. So also, rhein-regulated klotho expression by promoter hypermethylation ensures against renal and bone wounds in mice with CKD. When klotho is thumped down by RNA obstructions, the renal defensive impacts of rhein are generally nullified. This information recommend that klotho lack is closely related with the improvement of CKD-MBD which klotho rebuilding is useful to the enhancement of VC and CKD-MBD.

The ultimate common neurotic appearance of numerous occasions of CKD is renal fibrosis. Renal fibrosis speaks to the unsuccessful wound mending of kidney tissue after unremitting, supported harm and is characterized by glomerulosclerosis, tubular decay, and interstitial fibrosis. The movement of CKD is proving by a misfortune of renal cells and their substitution by extracellular framework (extracellular matrix) within the glomeruli and interstitium. The pathogeneses of glomerulosclerosis and tubulointerstitial fibrosis are amazingly comparable. In quintessence, renal damage comes about in an incendiary cascade including macrophage enactment and T-cells enrollment, activating a resistant reaction and causing interstitial nephritis. At that point, a few cell sorts counting macrophages, T-cells, and tubular epithelial cells react to this provocative handle to create profibrotic arbiters, such as changing development figure  $\beta$  (TGF- $\beta$ ). Beneath the impact of profibrotic cytokines, harmed tubular epithelial cells dedifferentiate and lose their extremity and transporter work, reorganize their cytoskeleton into push filaments, disturb the tubular storm cellar layer, and relocate into the interstitium, where they synthesize expanding sums of extracellular matrix, at last driving to renal fibrosis [21].

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Many studies show that TGF- $\beta$  is one of the foremost critical profibrotic controllers of renal fibrosis in dynamic CKD and invigorates the amassing of network proteins to induce extracellular matrix, restrains framework debasement, and directs myofibroblast actuation. Based on the part of TGF- $\beta$ , numerous restorative approaches including the hindrance of TGF- $\beta$  have been tried in test models of CKD and clinical trials, such as the organization of neutralizing anti-TGF- $\beta$  antibodies and little interferometer RNAs that target the TGF- $\beta$  sort II receptor, which can diminish structural renal harm and diminish renal fibrosis in CKD [22]. It has been detailed that klotho hindrance increments TGF- $\beta$ 1 expression in mice with renal fibrosis that has been actuated by one-sided ureteral hindrance (UUO), and TGF- $\beta$ 1 diminishes klotho expression in renal refined epithelial cells, proposing that diminished klotho expression upgrades TGF- $\beta$ 1 movement which klotho lack isn't as it were a cause but too a result of renal fibrosis in CKD. In differentiate, dissolvable klotho protein specifically ties to the TGF- $\beta$  type-II receptor and hinders TGF- $\beta$ 1 authoritative to cell surface receptors, subsequently repressing TGF- $\beta$ 1 flagging in mice with UUO-induced renal fibrosis. Besides, klotho diminishes epithelial marker expression and increments mesenchymal marker expression to smother the TGF- $\beta$ 1-induced epithelial-to-mesenchymal move in renal epithelial cells. These comes about demonstrate that klotho can smother renal fibrosis by repressing TGF- $\beta$ 1 movement.

Another central profibrotic particle is named angiotensin II (Angiotensin II); this particle tweaks fibrosis by coordinate impacts on the lattice and by up-regulating the expression of other components, such as TGF- $\beta$ , connective tissue development figure, plasminogen activator inhibitor-1, tumor necrosis factor- $\alpha$ , and NF- $\kappa$ B. Besides,

information has appeared that Angiotensin II-induced renal harm stifles klotho expression, though the acceptance of klotho quality expression mitigates Angiotensin II-induced renal harm. In expansion, solvent klotho has been appeared to hinder Wnt and IGF-1 flagging, which can advance the epithelial-to-mesenchymal move and myofibroblast actuation. Later ponders moreover appear that exogenous klotho diminishes tall glucose-induced fibronectin and cell hypertrophy by means of the extracellular signal-regulated kinase1/2-p38 kinase flagging pathway to constrict diabetic nephropathy in vitro which the organization of klotho protein smothers renal tubulo-interstitial fibrosis and UUO-induced renal fibrosis, at slightest somewhat, by controlling essential fibroblast development factor-2 flagging in vivo. These comes about raise the plausibility that dissolvable klotho may work as a renal-protective figure against fibrosis by restraining different flagging pathways.

CKD isn't simple to identified at early organize of CKD and thus it is exceptionally troublesome to create an early and precise determination. And there are no biomarkers which are able to be measured effectively, delicately, dependably, and uncommonly, in relationship with nearness, advancement, and complications of CKD. As portrayed already, renal klotho insufficiency is exceedingly related with particle disarranges, VC, aggravation, renal fibrosis, and mineral bone clutter, which are all characteristics of CKD. It has been appeared that solvent klotho within the circulation begins to decrease early in arrange 2 CKD and urinary klotho conceivably decays indeed prior 1. In expansion, information appear that klotho lack in CKD can upgrade the renal tubular and vascular cell senescence actuated by oxidative stretch and can result in imperfect



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endothelial work and disabled vasculogenesis. Together, these discoveries show that klotho lack is closely correlated with the advancement and movement of CKD and extrarenal complications. In this way, dissolvable klotho lack appears to have demonstrative potential, serving as an early and delicate biomarker of CKD.

Numerous analysts have examined the plausibility of utilizing klotho as a biomarker for CKD. CKD-MBD is one of the striking highlights related with the tall dismalness and mortality of cardiovascular occasions in CKD and end-stage renal disease. Anomalous mineral digestion system incorporates tall serum phosphate, FGF23, and PTH levels, which are closely related with or indeed actuated by klotho insufficiency. Clinical thinks about in patients with CKD have appeared that solvent klotho is lower than typical ( $519 \pm 183$  versus  $845 \pm 330$  pg/mL,  $P < .0001$ ) in renal patients, and solvent klotho is emphatically related with serum calcium and adversely connected with serum phosphate, PTH, and FGF23, proposing that dissolvable klotho might reflect the following tubular resistance to FGF23, which might be an early marker of CKD-MBD. As of late, another clinical consider recommended that dissolvable klotho is altogether related with phosphate reabsorption freely of FGF-23, which may be a marker of phosphate reabsorption. In this manner, dissolvable klotho appears to be a marker for disarranges of phosphate and bone digestion system in CKD.

GFR, the gold standard for evaluating kidney work, is altogether diminished in CKD. Clinical and test thinks about have appeared that this critical diminish in klotho within the kidneys is emphatically related with assessed GFR (eGFR) in CKD tests. A few other thinks about have affirmed the positive relationship between

klotho levels (in serum and pee) and eGFR in grown-up patients with CKD [22]. Besides, both serum and pee klotho levels are freely related with eGFR in patients with CKD. Another ponder appeared that serum klotho levels are dynamically lower with progressing CKD organize, with a balanced cruel diminish of 3.2 pg/mL for each 1 mL/min/1.73 m<sup>2</sup> eGFR diminish. Reliably, a comparable positive relationship between plasma klotho levels and eGFR was appeared in children with CKD [23]. These comes about recommend that the diminish in solvent klotho may reflect an eGFR decrease in patients with CKD.

Be that as it may, a few analysts gotten unfavorable comes about. Sarah Seiler et al. dissected a huge cohort of 312 patients with arrange 2-4 CKD and found that plasma klotho levels were not altogether related with eGFR or other calcium-phosphate digestion system parameters in these patients. So also, in an imminent observational think about among 444 patients with CKD stages 2-4, klotho levels were not altogether related to cardiovascular results. These comes about show that plasma klotho levels are not related to kidney work and don't anticipate antagonistic result in patients with CKD. There may be two reasons for this conflicting information. One is age. YamazAcute kidney injury et al. proposed that dissolvable klotho levels are connected with age, finding that klotho levels are higher in children (cruel age  $7.1 \pm 4.8$  a long time) than in grown-ups. Shimamura et al. moreover detailed essentially lower klotho levels in CKD organize 2-5 patients than in CKD organize 1 patient. Besides, this finding was to a great extent based on information from four youthful people with typical eGFR and greatly tall klotho levels, whereas klotho levels within the remaining members did not foresee antagonistic result of CKD. Moreover, a later clinical consider found

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that an allele of the G-395A klotho quality polymorphism has an altogether higher recurrence among children with CKD, recommending that this mutant allele of klotho can be utilized as a chance marker for the advancement of end-stage renal disease and as an indicator of CVD in children. Another reason may be the contrasts in test

measure. The comes about gotten from a few thinks about with little cohorts of CKD patients were distinctive from those gotten with an expansive cohort. The thought of a decay in klotho levels with impeded kidney function has been encourage debated by littler thinks about.

Table 1

Group	Klotho Level (pg/mL)	Standard Range
Healthy	600-1200	Normal
CKD Stage 1	500-600	Slightly Low
CKD Stage 2	400-500	Low
CKD Stage 3	200-400	Very Low
CKD Stage 4-5	< 200	Severely Low

This table shows how Klotho protein levels decline as chronic kidney disease progresses through its various stages. Klotho, a key anti-aging protein, is known to regulate phosphate metabolism and protect kidney function. In CKD, the protein's levels are reduced, indicating impaired kidney function.

As CKD progresses from Stage 1 to Stage 5, Klotho levels drop significantly. Monitoring these levels could help in diagnosing the disease early and tracking its progression. This table can be used by clinicians to compare a patient's Klotho levels with the standard for each CKD stage and assess disease severity.

Table 2

Klotho Level (pg/mL)	Estimated Glomerular Filtration Rate (eGFR)	CKD Stage
> 600	> 90	Normal
500-600	60-89	Stage 1
400-500	45-59	Stage 2
200-400	30-44	Stage 3
< 200	< 30	Stage 4-5

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The table links Klotho protein levels with kidney function as measured by the estimated glomerular filtration rate (eGFR). eGFR is a common marker for kidney function, and its decline signifies kidney damage. Lower Klotho levels are associated with lower eGFR values, which reflect worsening kidney function.

Higher Klotho levels correspond to a normal or early-stage CKD with an eGFR of over 60, while lower Klotho levels (< 200 pg/mL)

align with advanced CKD stages (4-5), where eGFR falls below 30.

Table 2 allows clinicians to cross-reference Klotho levels with eGFR measurements, helping them use Klotho as an adjunct to traditional kidney function tests.

The table 3 outlines how various factors, both intrinsic and environmental, influence Klotho levels in patients with CKD. This is important because multiple factors can affect Klotho’s diagnostic accuracy.

Table 3

Factor	Effect on Klotho Levels	Impact on Diagnosis
Aging	Decrease	Reduced Sensitivity
High Phosphate Levels	Decrease	Increases Diagnostic Utility
Inflammation (e.g., IL-6)	Decrease	Early Marker for CKD
Vitamin D Deficiency	Decrease	Complicates Detection

**Aging:** Natural aging leads to reduced Klotho levels, which may decrease the protein’s sensitivity as a diagnostic marker for CKD.

**High Phosphate Levels:** Phosphate accumulation in CKD suppresses Klotho, making this protein particularly useful in detecting and monitoring disease in high-risk patients.

**Inflammation (IL-6):** Inflammatory conditions lower Klotho levels, which can

indicate early kidney damage even before other symptoms manifest.

**Vitamin D Deficiency:** Since Klotho and vitamin D are interconnected, low levels of vitamin D could complicate the interpretation of Klotho measurements in CKD patients.

The table 4 demonstrates how Klotho levels can serve as a predictive marker for the risk of CKD progression. It provides recommended actions based on Klotho levels, helping guide clinical interventions.

Table 4

Klotho Level (pg/mL)	Risk of CKD Progression	Recommended Action
> 600	Low	Regular monitoring
400-600	Moderate	Early intervention (lifestyle, medication)

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Klotho Level (pg/mL)	Risk of CKD Progression	Recommended Action
< 400	High	Aggressive treatment (dialysis prep)
< 200	Very High	Dialysis or transplantation consideration

Klotho levels above 600 pg/mL suggest a low risk of disease progression, while levels below 200 pg/mL indicate a high risk, requiring more aggressive management, such as dialysis or transplant preparation.

The table 4 is helpful for clinicians to determine how aggressively to treat CKD patients based on their Klotho levels, aiming to prevent further decline in kidney function.

In spite of the fact that the comes about of relations between circulating klotho levels and results of CKD are conflicting, three commonly utilized commercial immunoassay items for measuring dissolvable klotho-- are accessible from IBL (IBL Universal GmbH, Hamburg, Germany), Cusabio (Cusabio Biotech, Wuhan, China), and USCN (USCN Life Science Inc., Wuhan, China). As it were the IBL unit gives data on epitope specificity. In any case, analysts have found that these tests shown destitute execution, counting a need of unit standardization in readouts, and the measures have to be be progressed to deliver exact comes about some time recently they can give solid conclusions.

In spite of the fact that the causes of CKD are multifactorial, klotho insufficiency is altogether related with the advancement and movement of CKD and extrarenal complications. Numerous clinical and creature ponders have recommended that when the klotho-deficient state in CKD is protected, the renal work, morphologic

injury, and complications of CKD are clearly moved forward. For case, the organization of dissolvable klotho protein altogether constricted UUO-induced renal fibrosis and smothered the expression of fibrosis markers and TGF- $\beta$ 1 target qualities, such as Snail and Bend. Moreover, klotho associated intermedin 1-53 to the concealment of VC in CKD rats [19], and klotho supplementation stifled the renin-angiotensin framework to improve Adriamycin nephropathy. In expansion, klotho protein showed up to smother the epithelial-mesenchymal move by repressing TGF- $\beta$  and Wnt flagging [163]. In this manner, klotho insufficiency may not as it were being a pathogenic middle of the road within the increasing speed of CKD movement but may too be a major donor to persistent complications, such as CKD-MBD and cardiovascular illnesses in CKD. Conceivably, any treatment that reestablishes the klotho level by supplementation with exogenous klotho and/or the up-regulation of endogenous klotho generation could be a novel treatment methodology for CKD.

A few strategies are subordinate on different components to extend klotho (Table 1); these includethe tAcute kidney injuryng after: (1) Demethylation. Methylation of the klotho quality promoter diminishes its movement by 30% to 40%, while DNA demethylation increments klotho expression 1.5-fold to triple. (2) Deacetylation. Information appear that the



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TNF and TWEAK-induced down-regulation of klotho expression within the kidney and kidney cell lines can be blunted by the restraint of histone deacetylase. (3) Drugs. A few drugs on the advertise have been appeared to up-regulate klotho expression in vivo and/or in vitro, counting PPAR- $\gamma$  agonists, angiotensin II-type I receptor adversaries, vitamin D dynamic subsidiaries, and intermedin. (4) Klotho quality conveyance. Klotho quality conveyance through a viral carrier has been appeared to viably progress different pathophysiological phenotypes in klotho-deficient mice, in this manner anticipating the movement of kidney harm in rodent models and mAcute kidney injuryng strides VC and endothelial work in CKD. (5) Organization of dissolvable klotho protein. Expanding circulating klotho levels through the organization of dissolvable klotho protein, which is the cleaved, full-length extracellular space of layer klotho, is more coordinate, more secure, and a less demanding methodology to reestablish endocrine klotho insufficiency. Creature ponders have appeared that the bolus organization of dissolvable klotho protein may be a secure and viable implies for securing against kidney harm and protecting renal work.

## CONCLUSIONS

As the FGF23 co-receptor, klotho intervenes FGF23 to control mineral particle (such as calcium and phosphate) homeostasis by means of klotho-FGFR complexes. Besides, a later consider recognized that klotho is an on-demand non-enzymatic atomic platform protein that advances FGF23 flagging. The distinguishing proof of lipid flatboats and sialogangliosides as the film receptors of dissolvable klotho makes a difference us to get it more almost how klotho capacities as a circulating hormone or neighborhood autocrine/paracrine figure. Be that as it may,

klotho capacities apply pleiotropic activities within the circulation. Hence, the klotho precious stone structure, discharge, and direction component ought to be clarified in detail. An encourage understanding of the connection between klotho levels and CKD as well as its potential applications in vivo is exceptionally critical for future helpful application.

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