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Original Article

Soluble α-Klotho in Chronic Kidney Disease: A Clinical Perspective

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ABSTRACT

Background: Chronic Kidney Disease (CKD) is associated with increased risk of cardiovascular disease & other complications. Soluble α-klotho expressed in distal tubules of kidney; is associated with mineral homeostasis by promoting phosphate excretion & calcium reabsorption. Studies show that klotho synthesis decreases with renal disease progression.
Objective: To estimate Serum levels of soluble α-klotho in participants with CKD & healthy control.
Methodology: In this study, (n=100) participants of age group 25-75years were divided 2 groups. Group I (n=75) subdivided into 5 sub-groups namely i, ii, iii, iv & v respectively according to KDQOI criteria for eGFR & Group II (n=25) comprising of healthy subjects were taken as control group. Serum samples were collected from both groups and evaluated for Blood Urea, Creatinine, Albumin, Vitamin D, Calcium & Phosphorus. Serum sample for soluble α-klotho was assayed in ELISA. Urine samples were collected for detection of proteinuria. Urine samples were evaluated for urinary albumin-creatinine ratio(UACR).
Results: Lower levels of α-klotho were associated with increased severity of CKD ($p<0.001$). It was significantly reduced in stage 2 as compared to stage 1 CKD & even further declined in stage 3-5. It was positively associated with eGFR ($r=0.654$ $p<0.001$). There was also statistically significant inverse association with serum creatinine ($r = -0.515$).
Conclusion: Decreased Serum levels of soluble α-klotho could have an advantage in early diagnosis and prognosis of disease complication.

Keywords: Chronic kidney disease (CKD), soluble α-klotho, prognostic marker. KDQOI.

INTRODUCTION

Chronic kidney disease (CKD) is a significant global public health burden, defined by a progressive and irreversible loss of renal function that increases mortality and morbidity, as well as social and economic costs.[1] Increased oxidative stress and abnormalities in mineral metabolism, such as hyperphosphatemia and hypocalcaemia, accompany chronic kidney disease (CKD), which worsens the prognosis and decreases survival.[2,3] Most patients with CKD die too soon, typically as a result of early onset age-related illnesses such as infections and cardiovascular disorders rather than actual renal failure. Patients frequently experience signs of early aging, including hypogonadism, skin shrinkage, and cognitive deterioration.[4] The KDIGO (Kidney Disease: Improving Global Outcomes) recommendations define chronic kidney disease (CKD) as kidney damage or an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m^2 for at least three months, regardless of etiology[3]. CKD is the third fastest-growing cause of death worldwide and is projected to rank fifth in terms of years of life lost(YLL) by 2040.[6]
In India, the prevalence of CKD has increased from approximately 11% (2011–2017) to >16% in recent times.[7]

Pathophysiology

Multiple factors, including glomerulosclerosis, interstitial fibrosis, and tubular atrophy, contribute to structural damage in patients with chronic kidney disease (CKD). Aging kidneys are particularly susceptible to these changes. Diabetes, hypertension, oxidative stress, and other metabolic risk factors often contribute to renal fibrosis.[4] Inflammatory mediators, including TNF-α and IL-6, are elevated as renal failure progresses, causing transcriptional alterations and persistent inflammation.[1]

CKD staging is based on eGFR levels (Table shown below) according to the KDIGO guidelines.[3]

Stage	eGFR	Remarks
I	≥ 90ml/min/1.73 m^2	Kidney damage with normal GFR
II	60-89ml/min/1.73 m^2	Mild reduced GFR
III	45-59ml/min/1.73 m^2	Mild to moderately reduced GFR
IV	15-29ml/min/1.73 m^2	Severely reduced GFR
V	<15ml/min/1.73 m^2	Kidney damage or ESRD

Albuminuria plays an important role in CKD risk stratification. Increased excretion of albumin in urine occurs even before a major eGFR decline, indicating early kidney damage. This is shown by UACR (urine albumin-creatinine ratio). UACR is categorised as follows –

Albuminuria categories		
A_1	A_2	A_3
Normal	Moderately increased	Severely increased
<30 mg/g	30-299 mg/g	≥300 mg/g

Klotho & CKD -

Klotho, first identified by Kuro-o et al. in 1997, is considered an anti-aging gene.[2] It is predominantly expressed in the cell membranes of renal tubular cells. Lower levels of soluble α-Klotho in the blood are caused by decreased Klotho synthesis, which results from impaired renal function.[1]

Klotho exists in two forms:

• Membrane-bound form — acts as a co-receptor for fibroblast growth factor-23 (FGF-23)

• Soluble form — released into blood, CSF, and urine by ADAM10/17 protease cleavage[8, 10]

s Klotho contributes to:

- Regulation of phosphate and vitamin D metabolism via FGF-23 signaling[9, 12]
- Enhanced calcium and potassium handling in distal tubules via TRPV5 & ROMK channels[12]
- Suppression of oxidative stress and inhibition of soft-tissue calcification[14]

CKD progression is associated with decreased Klotho transcription and protein shedding, contributing to CKD-mineral and bone disorder (CKD-MBD).[17]

MATERIALS AND METHODS

A cross-sectional analytical study was conducted in the Department of Biochemistry in collaboration with the Department of Nephrology, at a tertiary care center (VIMSAR, Odisha), over a period of 3months. One hundred participants were included in this study of age group 25-75years & were divided into two groups. Group I (n=75) was subdivided into five subgroups, namely i, ii, iii, iv, and v, according to the KDQOI (Kidney Disease Outcomes Quality Initiative) criteria[16] for eGFR, and Group II (n=25) comprising healthy subjects was taken as the control group.

Inclusion Criteria: Individuals with CKD and age and sex-matched healthy individuals.

Exclusion Criteria: Dialysis patients, prior renal replacement therapy, malignancy, polycystic kidney disease, liver disease, acute kidney injury, pregnancy, and refusal to participate.

After obtaining informed consent from all the participants, blood and urine samples were collected under aseptic conditions. Blood samples were collected in red-capped vials containing a clot activator and centrifuged at 3000 rpm for 10 min to separate the serum.

The serum was evaluated for biochemical parameters such as Serum Creatinine, Blood Urea Nitrogen, Albumin, Calcium & Phosphorus in Roche Cobas 311 biochemical autoanalyzer.

Serum Vitamin D levels were estimated using CLIA. Serum levels of soluble α-Klotho were estimated using an ELISA Scan Reader (sandwich technique) according to the manufacturer's protocol. UACR was calculated using urinary albumin and creatinine levels. The eGFR was calculated using the MDRD formula[16].

eGFR =175 × (Sr. creatinine×0.01131) $^{-1.154}$ ×(age)$^{-0.203}$ × [0.742 (if female)] × [1.1210(if patient is black)]

Statistical Analysis: -

Statistical analysis was performed using SPSS version 27.0. Continuous variables are expressed as mean ± standard deviation (SD). Groups were compared using ANOVA, and single univariate correlations were evaluated using independent t-tests. Pearson's correlation coefficient was also evaluated for various components, and a p-value < 0.05 was considered statistically significant. The correlation was graphically represented using scatter plots.

RESULT

Soluble α-Klotho levels were significantly reduced across CKD stages compared to those in the controls. The highest levels were observed in the controls (745.62 ± 181.24 pg/mL), which decreased progressively to stage V (386.93 ± 118.81 pg/mL). Albuminuria progressively increased and became significant from stage II onward, reaching macroalbuminuria in stage III.

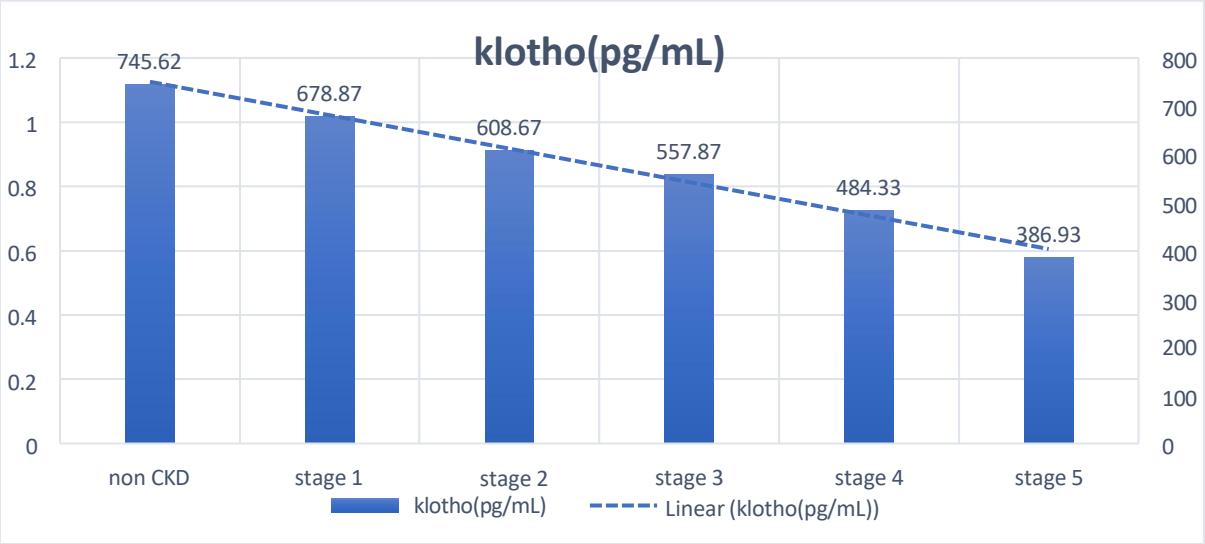
Alpha-Klotho exhibited: -

- Positive correlation with eGFR (r = 0.654, p<0.001)
- Negative correlation with serum creatinine, phosphorus and UACR (p<0.01)

Table 1 showing mean ± SD of different parameters in group 1 & group 2-

Parameter	Group 1					Group 2
	I(n=5)	II(n=7)	III(n=18)	IV(n-23)	V (n=22)	(n=25)
Age	41.7± 10.3	40.6± 12.3	57.0± 15.1	64± 12.8	61.1± 17.6	58.3± 16.44
SBP (mmHg)	132±10	137±13	144±19	146±20	140±26	128±12
DBP (mmHg)	80±8	85±9	76±14	80±12	69±23	84±10
α Klotho (pg/ml)	678.87± 226.05	608.67± 197.56	557.87± 170.65	484.33± 133.12	386.93± 118.81	745.62± 181.24
eGFR(ml/min/1.73m^2)	103.78 ± 8.9	76.10 ± 12.59	42.25 ± 9.67	23.85 ± 5.80	9.71 ± 2.79	108.6 ± 11.57
Sr.Creatinine (mg/dl)	0.89 ± 0.12	1.32 ± 0.16	2.18 ± 0.45	5.02 ± 0.82	8.64 ± 2.32	0.70 ± 0.14
Sr. Alb.(gm/dl)	4.7±0.3	4.3±0.6	3.8±0.6	3.3±0.4	3.1±0.4	5.02±0.24
Sr.Calcium (mg/dl)	9.3±0.3	9.0±0.6	8.6±0.6	8.2±0.7	7.9±0.8	9.74±0.43
Sr.P(mg/dl)	3.6±0.8	3.9±0.7	4.0±0.6	4.8±0.9	5.2±1.2	3.7±0.6
BUN (mg/dl)	12.31± 3.42	15.22± 4.01	25.60± 7.14	37.21± 9.62	55.54± 18.24	11.86± 3.42
UACR (mg/g)	20.5 ± 3.30	165 ± 78	444 ± 76	938 ± 221	1550 ± 214	6.71 ± 3.76

The bar graph shows decreasing trend of soluble α Klotho in healthy group & different stages of CKD.



The scatter plot shows linear regression analysis between soluble α Klotho & eGFR with r value = 0.654 indicating positive correlation.

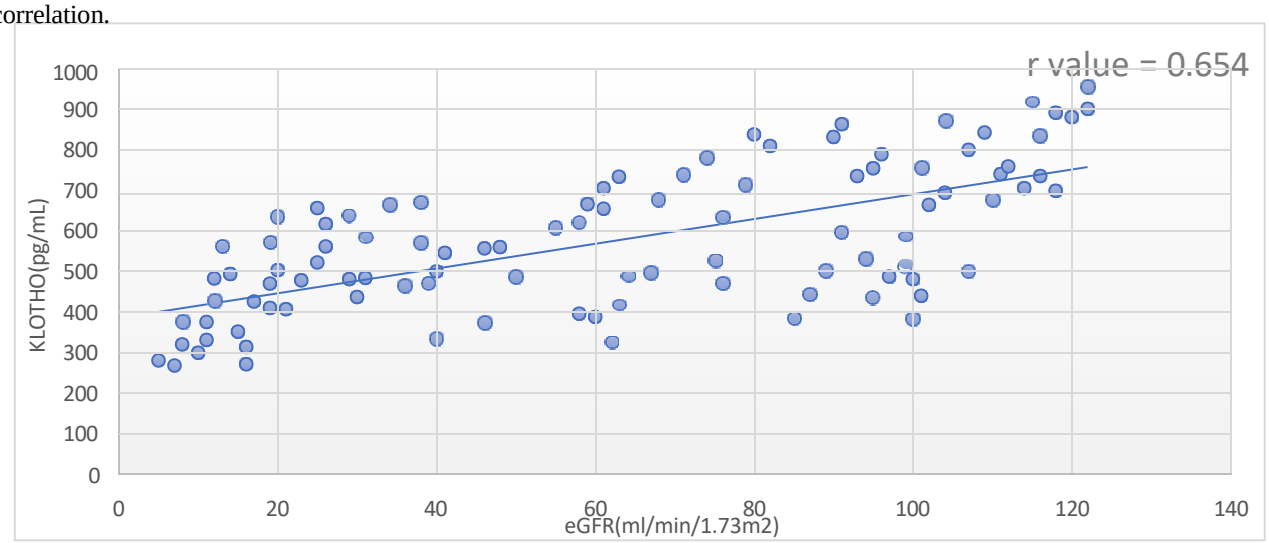


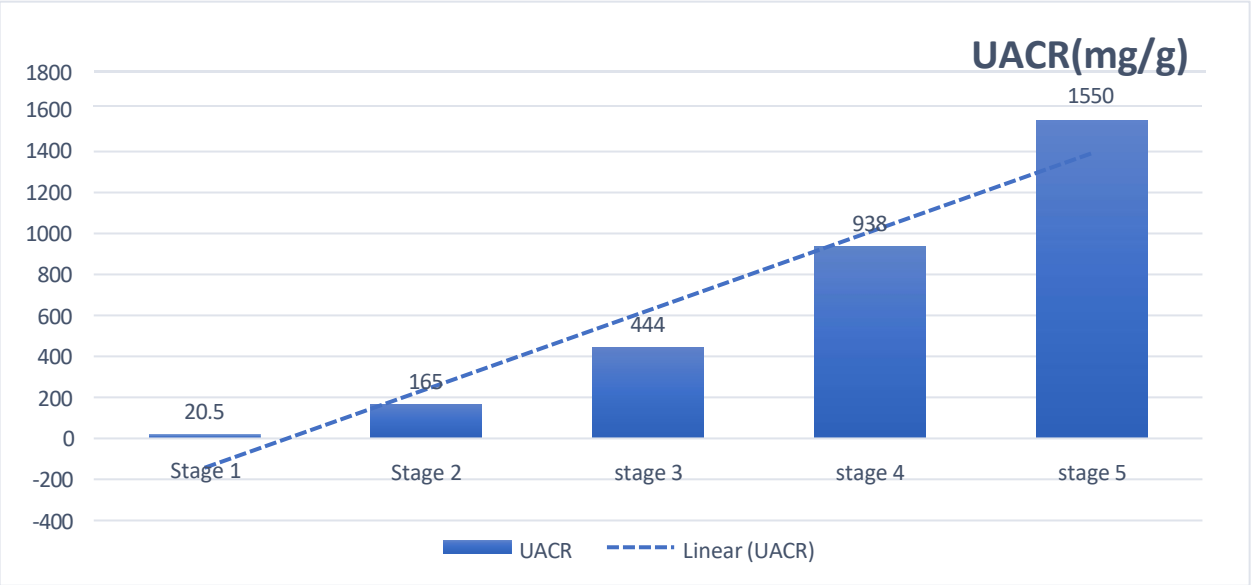
Table 2 shows association of various parameters of CKD with α Klotho. There is negative correlation between α Klotho & Serum Creatinine, Serum Phosphorus, UACR.

Parameter	**r value**	**p value**
eGFR	+0.654	<0.001*
Sr. Creatinine	-0.515	<0.001*
Sr. Phosphate	-0.462	<0.01*
BUN	-0.420	<0.01*
UACR	-0.504	<0.001*

Table 3 shows that prevalence of Vitamin D deficiency increases with advancing stage of CKD.

CKD Stage	**Deficiency (<20ng/ml)**	**Insufficiency (20-29ng/ml)**	**Sufficiency (>30ng/ml)**
1 (n=5)	20%(1)	40%(2)	40%(2)
2 (n=7)	28.5%(2)	28.5%(2)	42.8%(3)
3 (n=18)	50%(9)	33.3%(6)	16.6%(3)
4 (n=23)	60.8%(14)	30.4%(7)	8.7%(2)
5 (n=22)	77.3%(17)	18.2%(4)	4.54%(1)

The bar graph shows levels of UACR in different stages - albuminuria became significant (>30mg/g) from stage II & macro albuminuria (UACR > 300mg/g) was observed from stage 3 onwards.



DISCUSSION

The results of several previous investigations are consistent with the study's evident and steady reduction in soluble α-Klotho concentration with decreasing eGFR. Shimamura et al. showed a similar decline in Klotho levels as CKD stages advanced.[11] Conventional markers are not sensitive enough for the early identification of CKD. The potential of α-Klotho as a novel early biomarker is highlighted by the fact that declining α-Klotho levels can occur before overt changes in eGFR. The function of soluble Klotho in phosphate processing and renal tubular damage is evident in the negative correlations between it and phosphorus/UACR. This confirms the earlier findings of Yamazaki et al. and Huang & Moe[14,19]. Decreased Klotho expression in chronic kidney disease (CKD) may be a biomarker as well as a factor in the development and systemic consequences of CKD, such as arterial calcification and cardiovascular risk.

CONCLUSION

The present study demonstrated that serum soluble α-Klotho levels significantly declined with CKD progression, reflecting the loss of kidney function and disordered mineral metabolism. Soluble α-Klotho could serve as a useful predictive marker of disease progression in the early stages and a prognostic indicator in CKD. Large-scale longitudinal studies are required to establish its clinical utility in CKD risk stratification and therapeutic monitoring, which could be helpful in preventing complications and facilitating disease modalities.

REFERENCES

1. Levey AS, Coresh J. Chronic kidney disease. The lancet. 2012 Jan 14;379(9811):165-80.
2. Kuro-o M, Matsumura Y, Aizawa H, Kawaguchi H, Suga T, Utsugi T, Ohyama Y, Kurabayashi M, Kaname T, Kume E, Iwasaki H. Mutation of the mouse klotho gene leads to a syndrome resembling ageing. nature. 1997 Nov 6;390(6655):45-51.
3. Levin A, Stevens PE, Bilous RW, Coresh J, De Francisco AL, De Jong PE, Griffith KE, Hemmelgarn BR, Iseki K, Lamb EJ, Levey AS. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney international supplements. 2013 Jan 1;3(1):1-50.
4. Stenvinkel P, Larsson TE. Chronic kidney disease: a clinical model of premature aging. American journal of kidney diseases. 2013 Aug 1;62(2):339-51.
5. Levey AS, Stevens LA, Schmid CH, Zhang Y, Castro III AF, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J. A new equation to estimate glomerular filtration rate. Annals of internal medicine. 2009 May 5;150(9):604-12.
6. Foreman KJ, Marquez N, Dolgert A, Fukutaki K, Fullman N, McGaughey M, Pletcher MA, Smith AE, Tang K, Yuan CW, Brown JC. Forecasting life expectancy, years of life lost, and all-cause and cause-specific mortality for 250 causes of death: reference and alternative scenarios for 2016–40 for 195 countries and territories. The Lancet. 2018 Nov 10;392(10159):2052-90.
7. Varma PP. Prevalence of chronic kidney disease in India-Where are we heading?. Indian journal of nephrology. 2015 May;25(3):133.
8. Hu MC, Shi M, Zhang J, Quinones H, Griffith C, Kuro-o M, Moe OW. Klotho deficiency causes vascular calcification in chronic kidney disease. Journal of the American Society of Nephrology. 2011 Jan 1;22(1):124-36.

9. Scholze A, Liu Y, Pedersen L, Xia S, Roth HJ, Hocher B, Rasmussen LM, Tepel M. Soluble α-klotho and its relation to kidney function and fibroblast growth factor-23. The Journal of Clinical Endocrinology & Metabolism. 2014 May 1;99(5):E855-61.
10. Chen CD, Podvin S, Gillespie E, Leeman SE, Abraham CR. Insulin stimulates the cleavage and release of the extracellular domain of Klotho by ADAM10 and ADAM17. Proceedings of the National Academy of Sciences. 2007 Dec 11;104(50):19796-801.
11. Shimamura Y, Hamada K, Inoue K, Ogata K, Ishihara M, Kagawa T, Inoue M, Fujimoto S, Ikebe M, Yuasa K, Yamanaka S. Serum levels of soluble secreted α-Klotho are decreased in the early stages of chronic kidney disease, making it a probable novel biomarker for early diagnosis. Clinical and experimental nephrology. 2012 Oct;16(5):722-9.
12. Hu MC, Shiizaki K, Kuro-o M, Moe OW. Fibroblast growth factor 23 and Klotho: physiology and pathophysiology of an endocrine network of mineral metabolism. Annual review of physiology. 2013 Feb 10;75:503-33.
13. Lindberg K, Amin R, Moe OW, Hu MC, Erben RG, Wernerson AÖ, Lanske B, Olauson H, Larsson TE. The kidney is the principal organ mediating klotho effects. Journal of the American Society of Nephrology. 2014 Oct 1;25(10):2169-75.
14. Yamazaki Y, Imura A, Urakawa I, Shimada T, Murakami J, Aono Y, Hasegawa H, Yamashita T, Nakatani K, Saito Y, Okamoto N. Establishment of sandwich ELISA for soluble alpha-Klotho measurement: Age-dependent change of soluble alpha-Klotho levels in healthy subjects. Biochemical and biophysical research communications. 2010 Jul 30;398(3):513-8.
15. Sakan H, Nakatani K, Asai O, Imura A, Tanaka T, Yoshimoto S, Iwamoto N, Kurumatani N, Iwano M, Nabeshima YI, Konishi N. Reduced renal α-Klotho expression in CKD patients and its effect on renal phosphate handling and vitamin D metabolism. PloS one. 2014 Jan 23;9(1):e86301.
16. NKF K. DOQI Clinical Practice Guidelines for chronic kidney disease: evaluation, classification and stratification. Am J Kidney Dis. 2002;39(2).
17. Faul C, Amaral AP, Oskouei B, Hu MC, Sloan A, Isakova T, Gutiérrez OM, Aguillon-Prada R, Lincoln J, Hare JM, Mundel P. FGF23 induces left ventricular hypertrophy. The Journal of clinical investigation. 2011 Oct 10;121(11).
18. Koh N, Fujimori T, Nishiguchi S, Tamori A, Shiomi S, Nakatani T, Sugimura K, Kishimoto T, Kinoshita S, Kuroki T, Nabeshima YI. Severely reduced production of klotho in human chronic renal failure kidney. Biochemical and biophysical research communications. 2001 Feb 2;280(4):1015-20.
19. Huang CL, Moe OW. Klotho: a novel regulator of calcium and phosphorus homeostasis. Pflügers Archiv-European Journal of Physiology. 2011 Aug;462(2):185-93.