The relationship between soluble klotho and different biomarkers of diabetic kidney disease- a cross-sectional study

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Introduction and objectives

Soluble Klotho (S klotho) results after the cleavage of transmembrane klotho, the latter acting as a single-pass co-receptor of fibroblast growth factor 23 (FGF23) at tubular level. Data from animal models suggest some pleiotropic effects of S klotho such as independent phosphaturic effects at the tubular level or an inhibition of TGF beta mediated fibrogenesis. The purpose of this study was to assess in patients with diabetic kidney disease (DKD) the relationship between S klotho and other markers of CKD-MBD, with a tubular injury marker kidney injury molecule-1 (KIM-1) and with a marker of fibrogenesis connective tissue growth factor (CTGF).

Methods

SUBJECTS

Our study included 52 patients with previously diagnosed diabetic kidney disease (stages 1-5, mean eGFR 64.76+/-32.69ml/min)
-mean age 59.03+/-14 years ; 25 female, 27 male
•In every patient we obtained medical history (duration of diabetes mellitus, history of eGFR in the past 12 months
• Every patient was assessed biologically on the day of admission, and we obtained the following parameters: serum creatinine (mg/dl), serum calcium (mg/dl), phosphorus (mg/dl), iPTH (pg/ml), spot urinary albumin creatinine ratio (uACR- mg/g creatinine). We estimated the glomerular filtration rate (eGFR- ml/min/1.73sqm) using the CKD-EPI formula.

Delta eGFR
- We calculated the reduction in the estimated glomerular filtration rate as the difference between current eGFR and previous eGFR (12 months ago) divided through previous eGFR multiplied with 100, and we obtained the percentage of eGFR decrease. We obtained a mean reduction of eGFR of 19.23+/-15.01 %.

ELISA technique

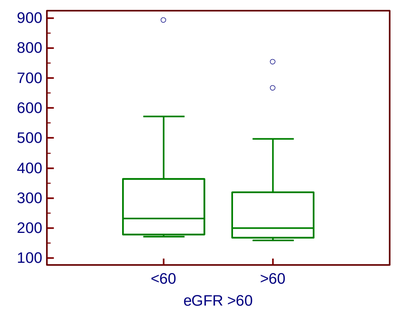
Blood samples collected from the patients on the day of admission were assessed using ELISA technique in order to obtain serum levels of: KIM-1, CTGF, soluble klotho, fibroblast growth factor 23 (FGF23).

	Mean value	Standard deviation
sKlotho (pg/ml)	311.58	216.76
FGF23 (pg/ml)	140.32	120.96
iPTH (pg/ml)	65.68	69.44
KIM 1 (pg/ml)	217.48	267.10
CTGF (pg/ml)	66.25	6.7

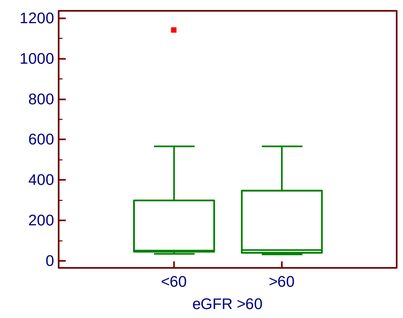
Results

We found a strong statistically significant correlation of S klotho with the tubular injury marker KIM-1(r=0.86, p=0.005), and also with serum Calcium (r=0.34, p=0.012) and a weak indirect correlation with iPTH (r=-0.22, p=0.045). There were no correlations between S klotho and serum phosphosrus, CTGF, renal function or uACR. On the other hand KIM-1 showed statistically significant correlations with other phosphocalcic markers: FGF-23 (r=-0.19, p=0.045), iPTH (r=0.38, p=0.014) and also with CTGF (r=0.64, p=0.016). Concerning the marker of fibrogenesis CTGF, its serum level correlated indirectly in a statistically significant manner with FGF23 (r=-0.51, p=0.012).

	sKlotho	KIM1
iPTH	**r=-0.22, p=0.045**	**r=0.38, p=0.014**
Serum Calcium	**r=0.34, p=0.012**	**NS**
Serum phosphorus	**NS**	**NS**
FGF23	**NS**	**r=-0.19, p=0.045**
CTGF	**NS**	**r=0.64, p=0.016**
Serum Creatinine	**NS**	**NS**
eGFR	**NS**	**NS**
uACR	**NS**	**NS**



sKlotho is higher in DKD patients with eGFR <60ml/min (328.9 vs. 299.5), however without statistical significance (p=0.7).



KIM1 is higher in DKD patients with eGFR <60ml/min (239.6 vs. 173.3), however without statistical significance (p=0.5).

In our patients we found a strong statistically significant correlation between sKlotho and the rate of reduction of eGFR/year r=0.83, p=0.0004.

Discussion

• Proximal tubular injury due to beginning diabetes in rats leads to elevated **plasma KIM-1** levels. [Alter et al., 2012]
• Hemodialysis patients with lower soluble **Klotho** have higher mortality. [Otani-Takei et al., 2015]
• CKD is a state of **Klotho** defficiency [Chang Hu et al., 2017]

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Conclusions

Our study indicates a relationship between KIM-1 and an increased level of S klotho, probably as a response to tubular injury. This process of tubular injury is possibly involved also in fibrogenesis, explained by the correlation between KIM-1 and CTGF. In our study we could not prove a direct relationship between S klotho and the marker of fibrogenesis CTGF. Future human studies are needed in order to reveal the relationship between tubular injury, fibrogenesis, S klotho in chronic kidney disease.

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