αKLOTHO AND FIBROBLAST GROWTH FACTOR 23 ARE NOT ASSOCIATED WITH THE DECREASE OF TUBULAR PHOSPHATE REABSORBTION IN EARLY CKD: EXPERIMENTAL AND CLINICAL STUDY

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INTRODUCTION AND AIMS

It is generally accepted that fibroblast growth factor 23 (FGF23) and αKlotho are implicated in the renal regulation of inorganic phosphate (Pi) excretion in chronic kidney disease (CKD). This concept is mainly based on experimental and clinical models of advanced stages of CKD, while data on associations of FGF23, αKlotho and Pi in early CKD are limited. The aim of the study was to investigate FGF23 and αKlotho levels and their associations with urinary Pi excretion in early kidney dysfunction.

EXPERIMENTAL STUDY

➢Model: 3/4 or 5/6 nephrectomy (NE) and sham-operated (s/o) spontaneously hypertensive rat (SHR)
➢The duration of experiments: 1 and 2 months

Tests

Phosphotonins: Klotho, FGFR1 in kidney (IHC), serum intact FGF23, intact PTH (ELISA)
Kidney function: serum urea (Ur), serum creatinine (sCr), creatinine clearance (CCr)
Phosphate methabolism: serum Pi (sPi), Pi excretion – uPi24, FEPi
Renal morphology: interstitial fibrosis (LM, morphometry)

Results

CCr decreased within 50% in 3/4 NE and 5/6 NE vs. s/o that corresponded to 2-3 stages of human CKD. Ur level was normal in s/o and «mild» to «moderate» in 3/4 NE and 5/6 NE (Ormrod D, Miller T., 1980). In NE rats interstitial fibrosis is developing gradually along with fall of CCr (fig. 1).

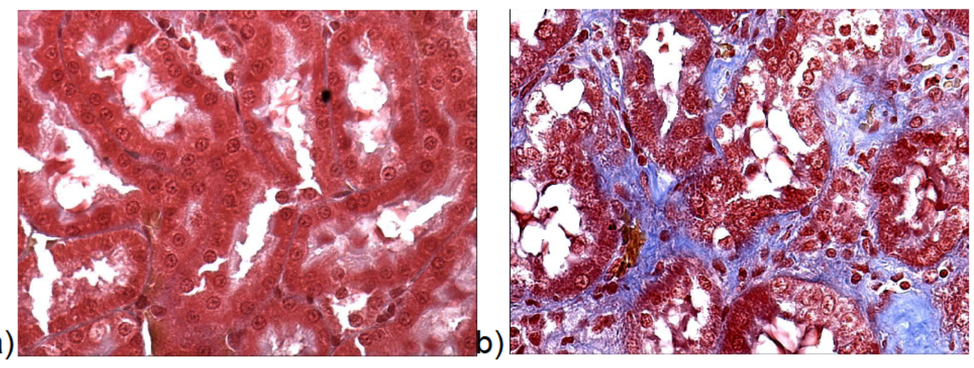

Figure 1. Masson's trichrome staining of renal cortex: s/o (a), 5/6NE (b)

The renal expression of αKlotho was significantly lower in all NE groups compared to s/o (table, fig. 2).

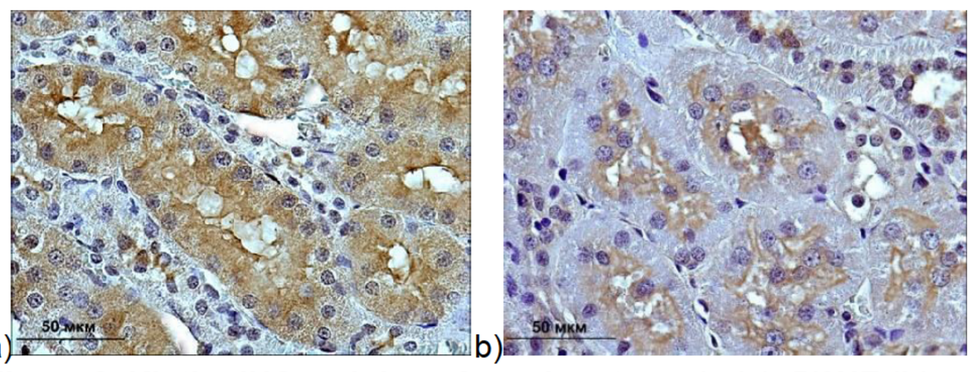

Figure 2. Klotho IHC staining of renal cortex: s/o (a), 5/6NE (b)

FGF23 level was significantly higher only in of 5/6NE 2 mo group vs. s/o 2 mo (table). There were no differences between PTH levels. At the same time, FEPi significantly increased in all NE vs. corresponding s/o animals. uPi24 was higher in all experimental groups vs. s/o, except 3/4NE 1 mo group.

Table. αKlotho, FGF23, urinary Pi excretion in experimental chronic kidney injury, # - p<0,05 in a comparison by groups

Group name (n)	1 Sham 1 mo (9)	2 3/4NE 1 mo (9)	3 5/6NE 1 mo (9)	4 Sham 2 mo (9)	5 3/4NE 2 mo (9)	6 5/6NE 2 mo (9)
FEPi, %	14.8	22.6#1	38.3#1,2	10.6	26.7#4	35.0#4,5
uPi24, mmol	0.55	0.88	0.95#1	0.41	0.98#4	1.05#4
FGF23, pg/ml	465.8	443.3	805.3	627.6	710.4	767.6#4
rKlotho, %	31.5	24.4#1	19.9#1	22.4#1	21.4	13.4#4,5
PTH, pg/ml	87.4	84.4	148.2	67.3	79.6	95.4

CLINICAL STUDY

➢ 80 patients (age 40.3, range 23-64) with primary glomerulopathies proven by biopsy
➢eGFR: 30-140 ml/min/1.73 m^2

Tests

Phosphotonins: renal Klotho – rKlotho (IHC), serum Klotho – sKlotho, intact FGF23, intact PTH and urinary Klotho (ELISA) standardized on the urinary creatinine - uKlotho/uCr
Kidney function: eGFR (CKD-EPI, 2009)
Phosphate methabolism: sPi, uPi24, FEPi
Renal morphology: interstitial fibrosis, tubular atrophy/dystrophy (LM)

Results

There are no significant differences of sPi and uPi24 in groups with eGFR 140-100, 99-70, 69-50 и 49-30 ml/min/1.73 m^2. FEPi level increased gradually eGFR of 99-70 ml/min/1.73 m^2 (p<0.001). Compared to eGFR 140-100 ml/min/1.73 m^2 rKlotho in tubular epithelium was significantly lower at eGFR 99-70 ml/min/1.73 m^2 (fig. 3, 4), sKlotho decreased at eGFR 69-50 ml/min/1.73 m^2 (fig. 4).

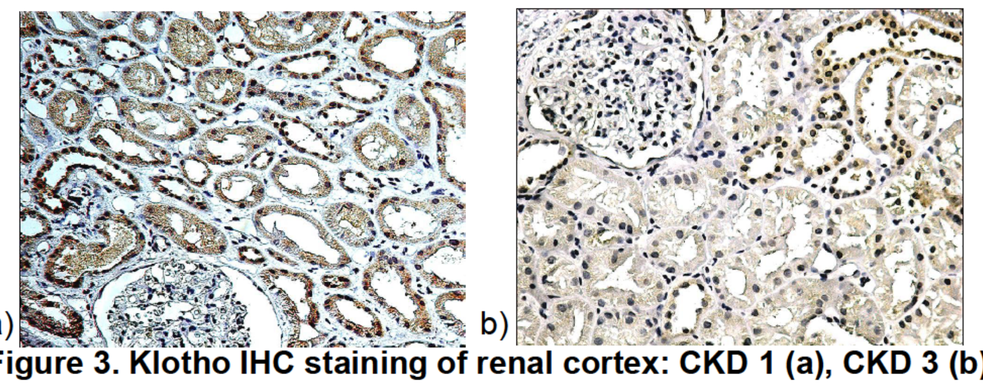

Figure 3. Klotho IHC staining of renal cortex: CKD 1 (a), CKD 3 (b)

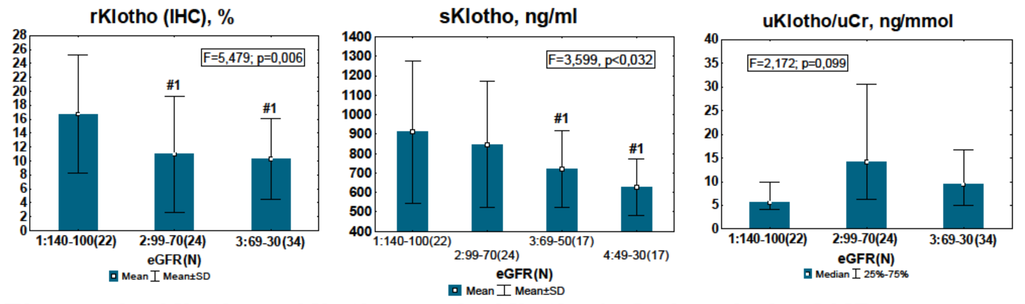

Figure 4. rKlotho, sKlotho and uKlotho/uCr levels in CKD

There are no significant differences of uKlotho/uCr level. sKlotho was associated with eGFR (r=0.35, p=0.002), interstitial fibrosis (r=-0.30, p=0.034), and glomerular sclerosis (r=-0.45, p=0.015). The level of PTH increased significantly at eGFR 99-70 ml/min/1.73 m^2, FGF23 – at eGFR 49-30 ml/min/1.73 m^2 compared to 140-100 ml/min/1.73 m^2 (fig. 5

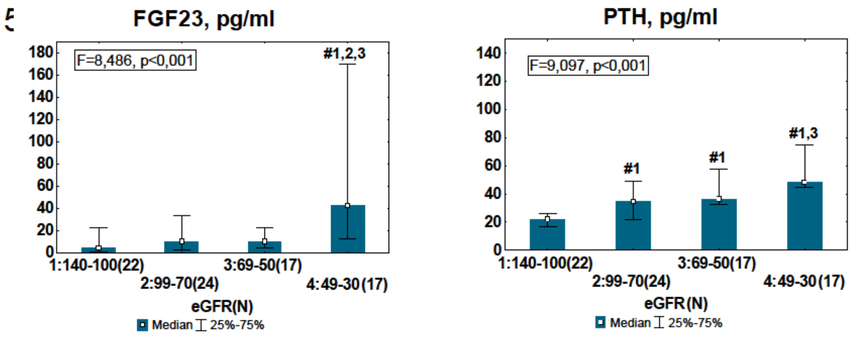

Figure 5. The level of FGF23 and PTH in CKD

In patients with eGFR ≥ 50 ml/min/1.73 m^2 no correlations were found between αKlotho/FGF23 system and indices of urinary Pi excretion, the level of PTH was associated with FEPi (r=0.28, p=0.024). In patients with eGFR < 50 ml/min/1.73 m^2 FGF23 was associated with sPi (r=0.53, p=0.028).

CONCLUSIONS

The decline of αKlotho in serum and kidneys occurs early in the course of CKD preceding the increase of FGF23 and apparently associates with tubulointerstitial injury. In early stages of CKD the alterations in tubular reabsorption and renal excretion of Pi is not associated with FGF23 and αKlotho.

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