DOWNREGULATION OF INTACT FIBROBLAST GROWTH FACTOR 23 (iFGF23) AND ASYMMETRIC DIMETHYL-ARGININE (ADMA) AND αKLOTHO UPREGULATION DURING ACUTE INFLAMMATION/SEPSIS IN STAGE 2-5 CKD PATIENTS

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Objectives:

High FGF23 and low αKlotho levels associate with systemic inflammation and reduced nitric oxide (NO) bioavailability in experimental models and in CKD patients. Such relationships are closely similar to those exhibited by ADMA, a methyl-arginine linked to inflammation and NO inhibition.
FGF23 and ADMA are inter-related in CKD patients but the response of these biomarkers and of αKlotho to acute inflammation /sepsis and the dynamics of this relationship haven't been investigated.

Methods:

Study population: 17 consecutive CKD patients of stage 2-5 (average eGFR 19.5±1.3 ml/min/1.73m^2).
Study design: longitudinal, assessment at 2 time points: at the peak of bacterial sepsis and after its complete resolution.
Measured biomarkers: serum carboxyl-terminal and intact FGF23 (cFGF23, iFGF23), αKlotho, ADMA,
biomarkers of inflammation (hs-CRP, IL-6, TNFα) and sepsis (procalcitonin)
nitrotyrosine (reflects NO synthesis and oxidative stress)
CKD-MBD biomarkers [PTH, 25(OH)D, 1,25$(OH)_2$D, Ca, Phosphate, serum iron, ferritin and albumin.
Statistical analysis: Normally distributed variables are summarized as mean±standard error (SE) and non-normally distributed as geometric mean and SE.

Results:

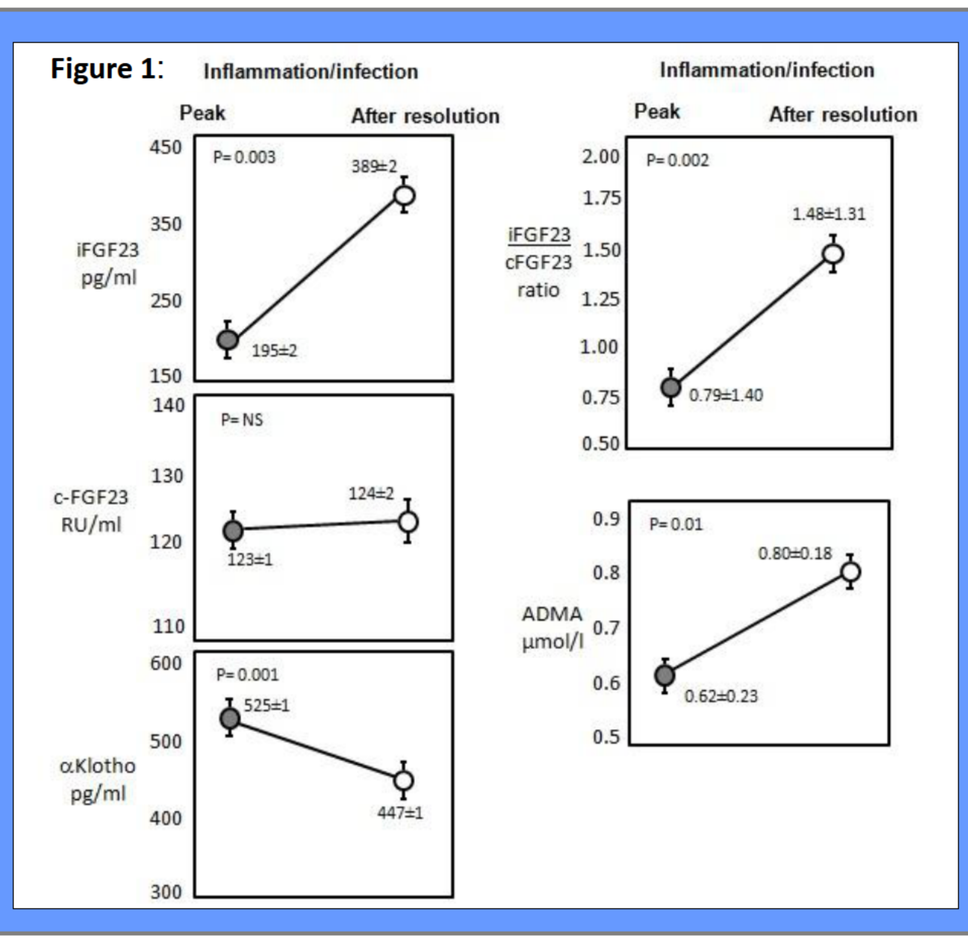
- At the peak of infection, biomarkers of inflammation/sepsis and nitrotyrosine were all very high and declined toward normal range after the resolution of infection (all P ≤0.01, except TNFα) (Table 1).
- iFGF23 at peak infection was 195±2 pg/ml and cFGF23 123±1 RU/ml. After the resolution of infection iFGF23 rose to 389±2 pg/ml (P=0.003) twice higher than at the peak infection while cFGF23 (124±2 RU/ml) remained unmodified (P=0.50). As a consequence, the iFGF23/cFGF23 ratio, an indicator of the proteolytic cleavage of FGF23 molecule was 0.79±1.40 at peak infection and markedly increased to 1.48±1.31 after the resolution of infection (P=0.02) strongly suggesting that inflammation/sepsis reversibly triggers FGF23 proteolysis (Figure 1).
- αKlotho was upregulated at peak infection (peak infection: 525±1 pg/ml; post-infection: 447±1 pg/ml P=0.001) (Figure 1).
- Changes in iFGF23 were closely paralleled by simultaneous changes in ADMA (Peak infection: 0.62±0.18 µmol/L; after infection resolution: 0.80±0.23 µmol/l, P=0.01) (Figure 1).
- Serum iron, ferritin and albumin showed the expected (opposite) response pattern to inflammation/infection (Table 1).
- eGFR (21±1.3 ml/min/1.73m^2) and CKD-MBD markers, except serum Ca did not change significantly throughout (Table 1).

Tables & Figures:

Table 1

	Peak of infection	Resolution of infection	p
Procalcitonin (ng/ml)	1.56 ± 1.52	0.40 ± 1.40	0.002
hs-CRP (mg/l)	105 ± 1	26 ± 1	<0.001
Nitrotyrosine (nMol/mL)	8.7±1.3	2.4±1.2	0.001
IL-6 (pg/ml)	82±1	12±1.4	0.001
TNFα (pg/ml)	12.5 ± 1.3	10.2±1.2	NS
eGFR (ml/min/1.72m^2)	19.5 ± 1.3	21.0 ± 1.3	NS
Iron(µg/dl)	16±1	38 ±1.2	0.001
Ferritin (ng/ml)	367±1	296±1	0.001
Albumin g/dl	3.1±0.1	3.4±0.1	0.007
PTH (pg/mL)	107 ± 1.3	96 ± 1.4	NS
25(OH)VD (nMol/l)	48.6 ± 6.8	50.3 ± 6.9	NS
1,25$(OH)_2$VD (pg/ml)	22.4 ± 3.9	18.1 ± 2.7	NS
Phosphate (mg/dl)	4.2 ± 0.3	4.7 ± 0.5	NS
Calcium (mg/dl)	8.7 ± 0.2	9.5 ± 0.1	0.003

Figure 1:



Conclusions:

Acute inflammation/sepsis activates αKlotho and suppresses both ADMA and the active form of FGF23, the latter effect being attributed to enhanced proteolysis of FGF23 whole molecule. iFGF23 and ADMA down-regulation and αKlotho up-regulation during acute sepsis may serve to sustain NO synthesis, a fundamental bactericidal compound in this acute condition.

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