CHRONIC KIDNEY DISEASE.
PATHOPHYSIOLOGY, PROGRESSION & RISK FACTORS - 1

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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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Introduction and Aims: 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 have not been investigated.

Methods: We sequentially measured 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), serum iron, ferritin and CKD-MBD biomarkers [PTH, 25(OH)D, 1,25(OH)2D] at the peak of bacterial sepsis and after its complete resolution in 17 stage 2-5 CKD patients (average eGFR 24±4 (SE) ml/min/1.73m2). 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 thereafter (all P<0.01). Serum iron and ferritin showed the expected (opposite) response pattern to inflammation/infection. iFGF23 at peak infection was 195±2 pg/ml and cFGF23 246±4 pg/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 (262±2 pg/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. Such response was mirrored by αKlotho levels which were upregulated at peak infection [peak infection: 525±1 pg/ml; post-infection: 447±1 pg/ml P=0.001]. Changes in iFGF23 were closely paralleled by simultaneous changes in ADMA (P=0.002). ADMA correlated directly with iFGF23 in an aggregated, appropriately weighted, linear regression analysis (n=34, β=0.52, p=0.002) while the inverse association of αKlotho with ADMA (β= -0.24) was much weaker and not significant (P=0.19). eGFR (29±7 ml/min/1.73m2) and CKD-MBD markers did not change significantly throughout.

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.