FGF-23 in Chronic Kidney Disease

Letter

Halankar et al. [1], have reported significant high levels of intact FGF-23 (iFGF-23) (19.0 fold, p=0.001) and tremendous increase in C-terminal FGF-23 (C-terminal FGF-23) (49.7 fold, p=0.001) in the circulation of CKD stage 5 (dialytic CKD) patients as compared to age and gender matched controls which did not decrease at six month on regular treatment of Calcium, Calcitriol and Phosphate binders. At recruitment, significant correlation between P and iFGF-23 (Spearman (rs) =0.317, p=0.028), was also observed. The above mentioned increase in levels of C-terminal FGF-23 have been suggested due to reduced renal clearance causing marked accumulation of C-terminal fragments in chronic hemodialysis patients [2] which in agreement with Goetz et al. [3], may interfere in the phosphaturic activity of the active iFGF-23 causing significant increase in P levels at the dialytic stage of CKD patients. Apart from the reduced renal clearance and accumulation of C-terminal fragments [2], other supposition suggested is, the increasing stimuli for FGF-23 production with deteriorating renal function could possibly overwhelm the capacity of the physiological inactivation mechanism that ordinarily controls the bioactive FGF-23 concentrations. It has been reported that increased production of FGF-23 by the bone may contribute to elevated levels in CKD and ESRD [4,5]. However, the biologic activity of C-terminal FGF-23 fragments remains a controversial topic and the mechanism postulated to explain the reduced renal clearance or decreased degradation rate of C terminal FGF-23 in CKD remains unclear.

Apart from the above findings, the authors would like to further add that in CKD stage 5 patients at six month, an inverse correlation between iFGF-23 and C-terminal FGF-23 (rs=-0.357, p=0.013) has also been observed. This indicates that the levels of iFGF-23 decreased with significant increased C-terminal FGF-23 levels. In order to transmit its signal, full length mature FGF-23 forms a heterotrimer complex with receptor FGF1Rc and co-receptor Klotho. Klotho binds to the C-terminal of FGF-23. Between the N-terminal and C-terminal domains of FGF-23 there is a cleavage site at 179 amino acid (amino acid number counting of signal peptide) that contains an RXXR motif which is the cleavage site for enzymes of the proconvertase-type of subtilisin or kexine type of the serine protease family. In its dynamics, active iFGF-23 is proteolytically cleaved at its C-terminal to produce inactive C-terminal and N-terminal fragments [6, 7]. Thus, C-terminal FGF-23 is produced by proteolytic cleavage of active iFGF-23 during functional dynamics of FGF-23.

In a study from our group on pre-dialytic CKD patients (CKD stage 1-4) [8], an inverse correlation between P and eGFR ((Pearson (r)=-0.467, p=0.021), direct correlation between P and C-terminal FGF-23 (rs = -0.464, p=0.022) and tremendous increase in C terminal FGF-23 levels (CKD stage 1,2-19.2%, p=0.001, CKD stage 3, 4 -32.3%, p=0.001) as compared to age, gender and BMI matched controls have been observed. This suggests that although within normal range, P levels increased with decrease in eGFR and up-regulated the FGF-23 levels. At CKD stage 1-4, at moderate to mild Kidney function and availability of α-Klotho [7], would take care of excretion of P, in spite of presence of C-terminal FGF-23 fragments. At six month, there was direct correlation observed between iFGF-23 and C-terminal FGF-23 (rs=0.543, p=0.007) (additional result). However, the fold increase of C-terminal FGF-23 above iFGF-23 (CKD stage 1, 2 -41.8 fold and CKD stage 3, 4 -60.6 fold) and correlation between P and C-terminal FGF-23 at recruitment, again suggests an additional source of only C-terminal FGF-23, independent from functional dynamics of co-transport inhibitory mechanism, which needs to be identified.
References


