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FGF23, IRON STATUS AND VITAMIN D METABOLISM IN CHRONIC KIDNEY DISEASE

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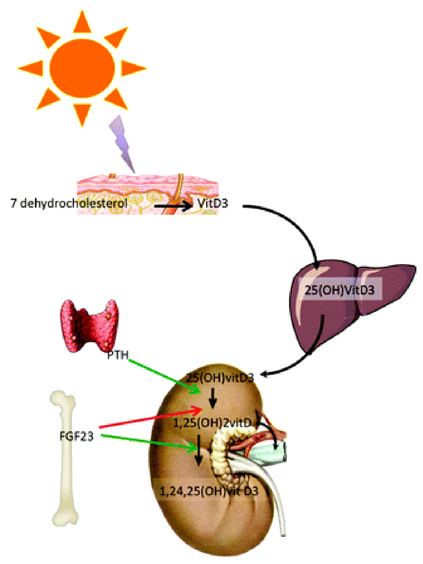
Introduction

Fibroblast growth factor-23 (FGF23) is a major regulator of phosphate and vitamin D metabolism often elevated in genetic hypophosphatemic disorders and in chronic kidney disease (CKD). In the kidney, FGF23 induces urinary phosphate excretion and reduces synthesis of 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) by down regulating 1α-hydroxylase and upregulating 24-hydroxylase activity[1].

However, Dai et al.[2], showed that serum concentrations of the 25(OH)D metabolite $24,25(OH)_2D$ are actually lower in CKD animals than in wild-type controls with similar results in CKD patients.

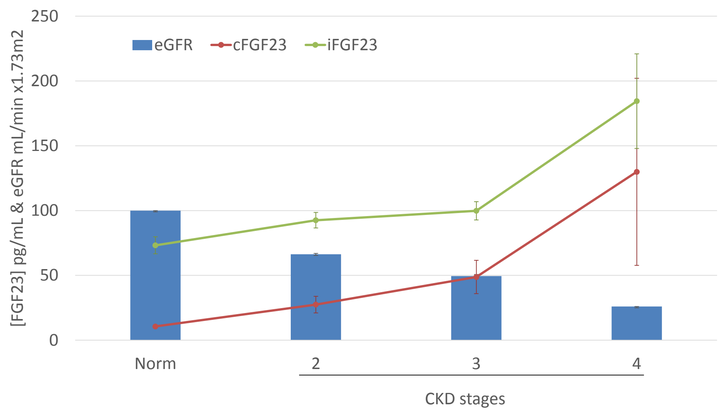


from Prié and Friedlander CJASN 2010[5]

Objectives:

- Determine vitamin D metabolism in CKD patients and its association with FGF23 concentrations.

FGF23 in CKD



Graphs showing the concentrations of c-terminal and intact FGF23 in CKD stage 2 to 4.

Parallel increase of intact and c-terminal FGF23 concentrations as eGFR decreased especially in patients with end-stage renal disease (stage 4 and over) usually regarded as a compensatory response to hyperphosphatemia or phosphate overload.

Methods

❖ Samples

Randomized samples from patients with chronic kidney disease (CKD; eGFR < 70 ml/min/1.73 m2) and controls (eGFR >100 ml/min/1.73 m2).

Samples were anonymised to the researchers at point of access in accordance with generic ethical approval

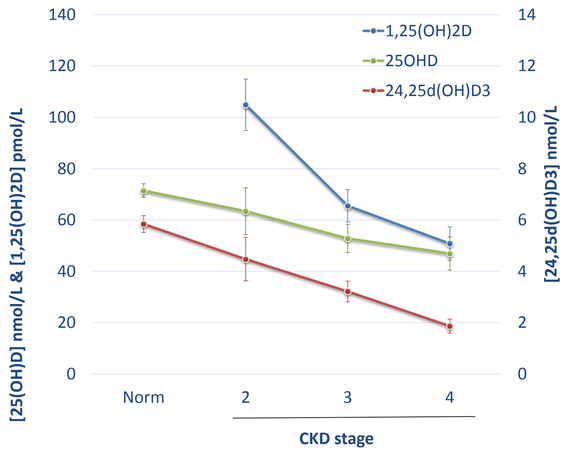
❖ Assays

- Intact FGF23 (cat# 60-6600) were two-site enzyme-linked immunosorbent assay (ELISA) 2nd generation from Immunotopics Inc., CA.
- c-terminal FGF23 (cat# BI-20702) was a sandwich enzyme immunoassay from Biomedica. Concentrations were calculated using 1pmol/L = 0.133pg/mL.
- 25 hydroxyvitamin D ($25(OH)D_2$ and $25(OH)D_3$) and it's metabolite 24,25 dihydroxyvitamin D_3 ($24,25(OH)_2D_3$) were measured by LC-MS/MS.

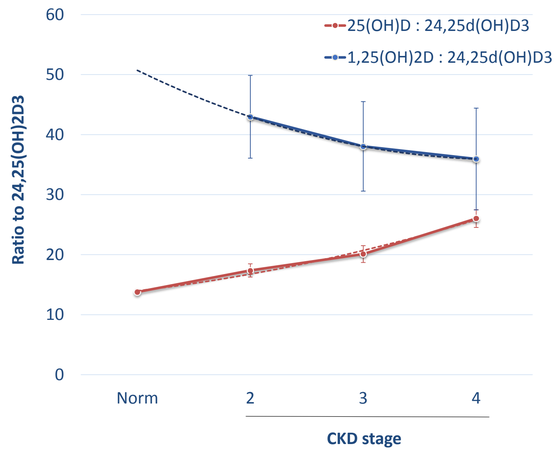
❖ Statistics

- Assay results were compared using Passing Bablock and Bland-Altman analyses.
- Concentrations were compared using one-way ANOVA. Trends were estimated using linear regression analysis
- SPSS for windows version 22.0.0.1 was used and results were considered statistically significant for $p<0.05$ [*$p<0.05$; ** $p<0.01$; ***$p<0.001$].

Vitamin D and FGF23 in CKD



Comparison of the grand means (±SEM) of serum 25(OH)D, serum $1,25(OH)_2D$ and $24,25(OH)_2D3$ between CKD patients (n=74, stage 2 to 4) and non-CKD (n=79) controls.



Comparison of the ratios of serum 25(OH)D and serum $1,25(OH)_2D$ to $24,25(OH)_2D3$ between CKD patients (n=74, stage 2 to 4) and non-CKD (n=79) controls.

Decreased concentrations of 25(OH)D, 1,25(OH)2D and $24,25(OH)_2D$. Increase ratio [25(OH)D]:[$24,25(OH)_2D3$]. Concentrations of FGF23, both C-terminal and intact, increased with decreasing kidney function. Both iFGF23 and cFGF23 correlated with the ratio 25(OH)D:24,25(OH)2D3 (Pearson's rho = 0.190 and 0.204, $p<0.05$, respectively) and iFGF23 also significantly correlated with 24,25(OH)2D3 (Pearson's rho = -0.323 $p<0.01$)

Conclusions

❖ The c-terminal FGF23 assays measure both cFGF23 and iFGF23, however we observed lower concentrations of cFGF23 than iFGF23, suggesting that the assays are measuring different forms of the protein and/or the specificity of the antibody used is different.

❖ Limited substrate (25-hydroxyvitamin D) availability to the enhanced renal Cyp24a1 could reduce 24,25-dihydroxyvitamin D production. However, the hepatic capacity to synthesize 25-hydroxyvitamin D was intact

❖ The ratio of 25(OH)D: 24,25(OH)2D is markedly elevated and increases as CKD progresses suggesting a relatively lower catabolic rate of 25(OH)D towards its $24,25(OH)_2D$ metabolite . This may be in an attempt to allow ongoing synthesis of 1,25(OH)2D continuing its biological effects. The significant correlations of FGF23 with the $24,25(OH)_2D3$ and the ratio 25(OH)D:$24,25(OH)_2D3$ suggest a potential role for FGF23 in the regulation of 24-hydroxylase in CKD. It would appear that the effects of FGF23 on vitamin D metabolism in CKD are greater than the effects of PTH and so this data adds further to the proposals that the early management and prevention of the increase of FGF23 in CKD may be beneficial in preventing CKD-BMD.

References:

1- Quarles LD. Nat Med. 2011;17:428–430 **2**-Fliser D, Kollerits B, Neyer U, et al. J Am Soc Nephrol. 2007;18:2600–2608. 2- Dai B, David V, Alshayeb HM, Showkat A, Gyamlani G, Horst RL, Wall BM, and Quarles LD. Kidney Int. 2012; 82(10): 1061–1070.