Effects of vitamin D supplementation on markers of bone and mineral metabolism in pediatric patients with early and late CKD

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Objectives

The effects of vitamin D supplementation on CKD-MBD (besides on iPTH levels) are largely unknown. We investigated the effects of vit. D suppl. on biomarkers of CKD-MBD in two patient cohorts with early and late CKD derived from a randomized trial on ergocalciferol suppl. (ERGO-trial, Shroff et al., CJASN 2012) and the 4C study cohort.

Methods

80 vitamin D-deficient (25(OH)D ≤75 nmol/L) pts. with CKD 2-4 started on vit. D suppl. or
not were enrolled from the ERGO-trial (40 pts. randomized either to ergocalciferol suppl. or placebo) and the 4C cohort (20 pts. started on cholecalciferol, 20 controls matched by age,
sex, eGFR, and serum calcium).
Serum levels of Klotho, intact/c-terminal-FGF23, and sclerostin were assessed at baseline
and after a median period of 6 mo. (range 4-12) using age- and sex-related standard deviation scores (SDS).

Results

Patient characteristics (Table 1)

4C patients presented with more advanced CKD, and consequently more pronounced biochemical abnormalities compared to ERGO patients.

Table 1	ERGO	4C	p
n	40	40	
Age (years)	9.13 (5.12)	12.66 (3.29)	<0.001
Male (%)	62.5	62.5	1.000
Height SDS	-0.81 (1.75)	-1.66 (1.14)	0.012
eGFR (ml/min * 1.73 m²)	54.8 (14.4)	24.3 (8.0)	<0.001
CKD (%) 2 3 4 5	 39.5 52.6 7.9 0	 2.6 12.8 82.1 2.6	<0.001
CAKUT (%)	92.5	65	0.006
Serum calcium (mmol/L)	2.42 (0.12)	2.32 (0.22)	0.016
Serum phosphate (mmol/L)	1.47 (0.22)	1.60 (0.31)	0.031
iPTH (pmol/L)	4.10 [2.50, 5.62]	15.05 [8.58, 44.04]	<0.001
Ca-based phosphate binders (%)	12.5	35	0.036
Ca-free phosphate binders (%)	0	2.5	1.000
Serum bicarbonate (mmol/l)	23.8 (2.2)	21.1 (3.6)	<0.001
Serum albumine (g/L)	43.6 (3.3)	39.8 (5.0)	<0.001
Albuminuria (g/mol creatinine)	1.8 [1.0, 4.6]	65.0 [15.7, 193.8]	<0.001
Makroalbuminuria (%)	8	65	<0.001

mean (standard deviation); median [interquartile range]

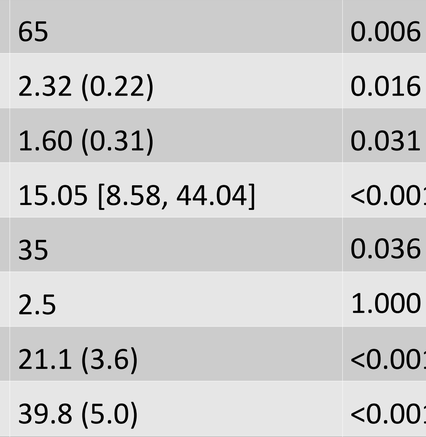
Efficacy of vitamin D supplementation

Vitamin D dosages were higher (median 1770 IU/day vs. 1099 IU/day) and duration of Tx was longer (289 vs. 212 days) in the ERGO group compared to the 4C group (each p<0.001). 25(OH)D levels were normalized in 14/20 ERGO pts. and in 8/20 4C pts., respectively (p<0.05). Final 25(OH)D levels correlated with body size related vitamin D dosage, age, eGFR, albuminuria and presence of macroalbuminuria.

Table 2: Determinants of final 25(OH)D levels

	r	p
Total dose / m²	0.53	<0.001
Total dose / kg	0.56	<0.001
Daily dose / m²	0.49	0.001
Daily dose / kg	0.53	<0.001
Age	-0.35	0.027
eGFR	0.43	0.007
Albuminuria	-0.42	0.008
Makroalbuminuria	-0.35	0.029

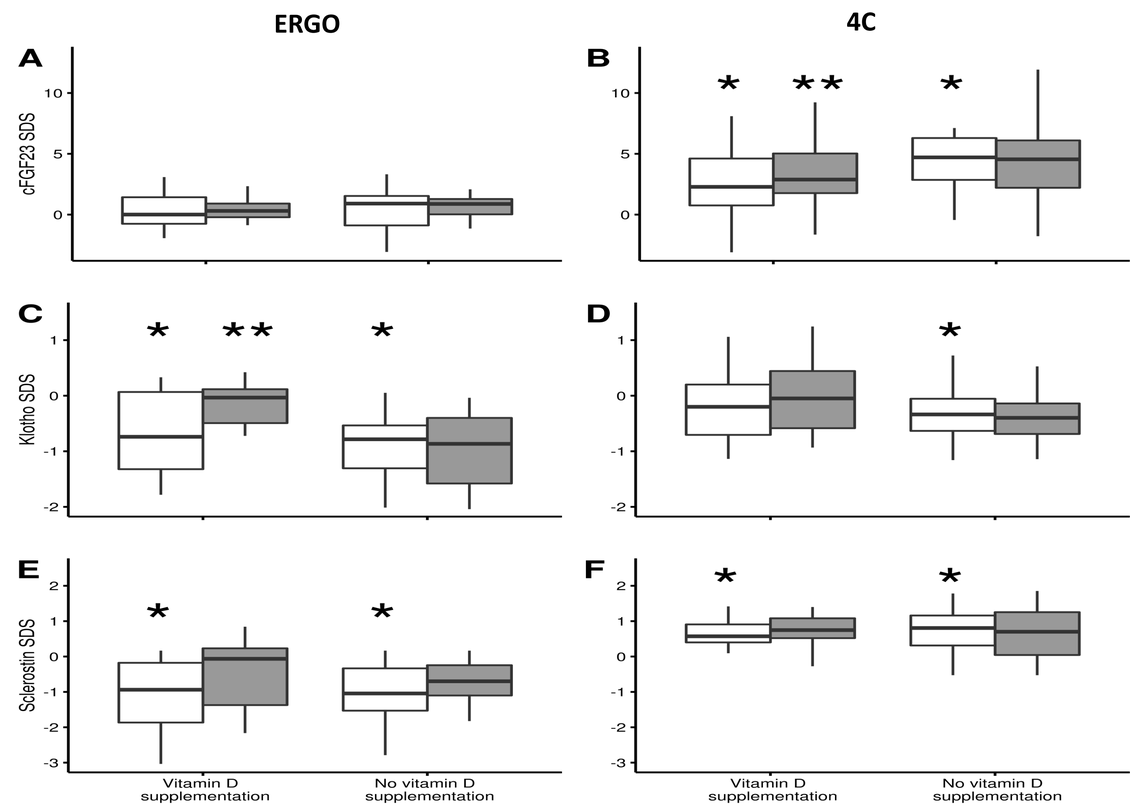
Fig 1: Change in 25(OH)D and Vitamin dosage



Effects of vitamin D supplementation on bone biomarker

Vitamin D suppl. did not affect S-Ca, phosphate, iPTH & $HCO3^-$ levels (not shown). FGF23 levels were further increased in 4C, but not in ERGO pts. (Fig. 2). Klotho and sclerostin levels were normalized in ERGO pts. and remained unchanged in 4C.

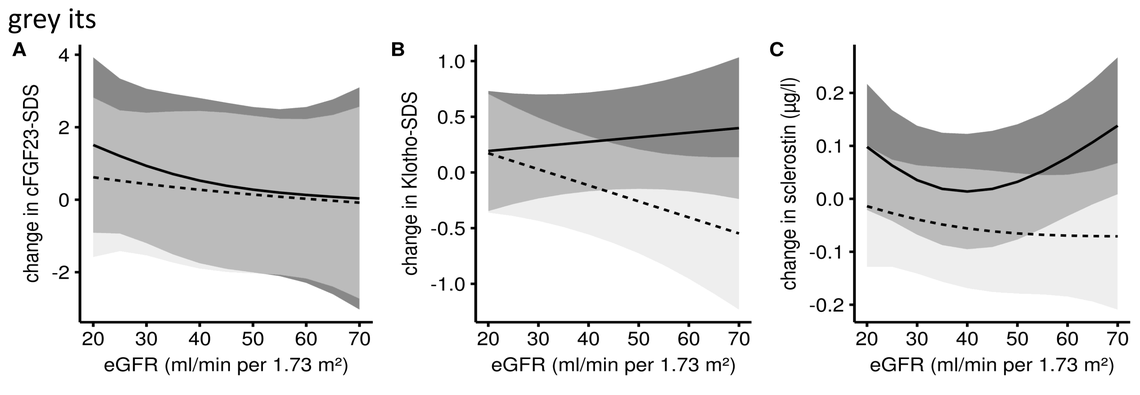
Fig. 2: Markers of bone metabolism at baseline (white) and at the end of observation (grey). * p<0.05 vs. healthy children; **p<0.05 vs. baseline values.



Changes in bone biomarkers as a function of eGFR

The increase in FGF23 SDS was higher in vitamin D treated pts. compared to c at eGFR 20 - 40 ml/min per 1.73 m² (n.s.). Positive changes for Klotho SDS and sclerostin levels were noted in vitamin D treated pts. and negative changes in controls. Significant group differences were noted for Klotho at eGFR 40 - 70 per 1.73 m² and for sclerostin at eGFR 60 - 70 ml/min per 1.73 m².

Fig. 3: Changes in bone biomarkers in vitamin D treated patients in comparison to controls Solid line denotes vitamin D group, dark grey its 95% CI; dashed line denotes control, light grey its



Multiple linear regression analysis

Outcome	Predictor	Beta coefficient	P-value	Adjusted R^2
Final 25(OH)D	 Age Daily dose/m²	 -2.248 0.013	 0.044 0.016	0.296
Delta 25 OH(D)	 Daily dose/m²	 0.018	 0.001	0.216
Delta Klotho (SDS)	 25(OH)D > 75 nmol/L	 0.698	 0.010	0.140
Delta Sclerostin (SDS)	 25(OH)D > 75 nmol/L	 0.013	 0.019	0.114

Conclusions

The efficacy of vitamin D supplementation is associated with body size related vitamin D dosage in pediatric CKD patients. Vitamin D supplementation normalizes Klotho and sclerostin levels in patients with mild CKD, but further stimulates FGF23 levels in advanced CKD.

*supported by a ESPN grant (# ESPN 2014.3)