ESPN CKD-MBD Working Group

Title of the study:

Effect of vitamin D supplementation on bone/mineral metabolism and immune system in children with early CKD (stage 2-3)

Background:
Children suffering from chronic-kidney disease (CKD) are prone to develop alterations of mineral and bone metabolism resulting in long-term sequel, i.e. growth failure, bone deformities, and ectopic calcifications. The alterations of bone and mineral metabolism in these patients are complex and have recently been termed CKD-mineral and bone disorder (MBD) (1-4). Vitamin D deficiency (i.e. 25OHD levels < 75nmol/L) is widespread prevalent in the general population and in children suffering from CKD (approx. 50-80%), and is an important contributor to CKD-MBD (5-7). Vitamin D supplementation is recommended according to current guidelines (KDOQI) in any CKD patient presenting with low 25OHD levels, but data on controlled trials in children are limited (8). Recently, the efficacy of vitamin D substitution on the prevention of secondary hyperparathyroidism (HPT) was investigated in 47 children with CKD stage 2-4 (9). Vitamin D supplementation was preventive for development of 2nd HPT in children with CKD stage 2-3, but not in patients with CKD stage 4. In this study patients with vitamin D deficiency were supplemented with vitamin D (ergocalciferol) according to KDOQI guidelines and investigated over a period of 24 months. Vitamin D does not only act via metabolism to active vitamin D (calcitriol) but also exerts many autocrine/paracrine actions. Indeed, vitamin D deficiency is associated with immunodeficiency, and an increased risk for cardiovascular disease, diabetes mellitus and cancer (5). Vitamin D has immunomodulatory effects with respect to the antibacterial innate immune system (10). However, data are coming mainly from epidemiological studies in the general population and effects of intervention with respect to vitamin D supplementation were rarely performed. A recent study in adult hemodialysis patients revealed no effect of vitamin D supplementation on Monocyte subsets during a treatment period of 12 weeks, but no comprehensive assessment of the immune system was done (11). So far no data on the effects of vitamin D supplementation in children with mild CKD are available with respect to mineral and bone metabolism (beside PTH levels) and the immune system.

Hypothesis:
Supplementation of vitamin D in children with early CKD (stage 2-3) has beneficial effects on surrogate markers of CKD-MBD and the immune system:

- Beneficial effects on bone and mineral metabolism (CKD-MBD)
- Effects on the immune system

Primary endpoint:

- Markers of osteoblast (total and bone alkaline phosphatase), osteoclast (TRAP5b, osteoprotegerin and RANK-L, and osteocyte activity (sclerostin), and mineral metabolism (FGF-23, soluble Klotho, 25OHD, calcitriol, 24,25-dihydroxyvitamin D, PTH)

Secondary end-points:

- Markers of immune system and iron homeostasis: hepcidin, cathelicidin, % of regulatory T cells
- Inflammatory markers (high sensitivity CRP, IL-6)
- Incidence of infections (viral, bacterial)
- Casual BP (SD-scores), 24h ABPM if possible
- Markers of renal failure progression: urinary albumin/creatinine ratio, creatinine (to calculate delta GFR)

Study design: prospective observational cohort study

Inclusion criteria:

- Children (age 1-17 years) with CKD stage 2 or 3
- No actual vitamin D treatment (≥ 3 months; native or active vitamin D)
- Start of vitamin D supplementation due to vitamin D deficiency (i.e. 25OHD level < 75 nmol/L) according to current guidelines (KDOQI)

Exclusion criteria: Age < 1 year or > 17 years, liver dysfunction, secondary hyperparathyroidism requiring treatment with active vitamin D according to current guidelines (KDOQI), i.e. PTH > 3fold upper normal range of the local lab, concomitant glucocorticoid treatment or other drugs potentially affecting vitamin D metabolism

Number of patients: n=60 assuming a drop-out rate of 10%. A pilot study will be done using the 4C-study population in order to make a calculation.

Study Protocol:
Patients presenting with vitamin D deficiency (i.e. 25OHD level < 75 nmol/L) receive vitamin D supplements (cholecalciferol) according to KDOQI guidelines (Fig. from Shroff et al (9)):

Intensive replacement phase (3 months)

Age < 1 year – 600 IU daily = 0.3ml/day
Age ≥ 1 year –
25(OH)D 40 – 75 nmol/L – 2000 IU/day = 1ml/day
25(OH)D 12.5 – 40 nmol/L – 4000 IU/day = 2ml/day
25(OH)D <12.5 nmol/L – 8000 IU/day = 4ml/day

Maintenance phase

Age < 1 year – 400 IU daily = 0.2ml/day
Age > 1 year – 2000 IU daily = 1ml/day

During the intensive replacement phase (3 months) patients will be visited at 0, 6, and 12 weeks. Follow-ups will be done three and nine months later. At each visit a physical examination will be done, history will be taken with respect to bacterial and viral infections, and blood will be drawn (see table).

	0 week	6 weeks	12 weeks	24 weeks	12 mo.
History/physical examination	X	X	X	X	X
Vitamin D and Ca/P metabolism[1]*	X	X	X	X	X
Bone panel[2]	X	X	X	X	(X)
Immune panel[3]	X	X	X	X	
24h ABPM	X		X		
eGFR, $U_{Alb, Ca, Crea}$*	X		X	X	X

1 = 25OHD, Ca, P, total AP, iPTH

2 = bone alkaline phosphatase, TRAP5b, osteoprotegerin, RANK-L, sclerostin, cFGF-23, soluble klotho, calcitriol, 24,25-dihydroxyvitamin D

3 = hepcidin, cathelicidin, % of regulatory T cells (only some centers), high sensitivity CRP, IL-6

* = local lab?

Recruitment period: 18 months

Intervention period: 3 months (vitamin D, intensive replacement phase), with a follow-up at 6 and 12 months

Total duration of the study: 30 months

Methods:
eGFR will be estimated according to the formula of 2009 (JB please add reference)
Bone markers will be centrally assessed in Hannover and London
Markers of immune system will be assessed in Lyon

Statistics:

Data on markers of CKD-MBD and BP will be presented as SD-scores if applicable (12). Power calculation with respect to primary endpoint will be done after finishing the pilot study.

References:

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