Activities of the ESPN CKD-MBD Working Group

Background: Children with 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 (CKD-MBD). Both, vitamin D deficiency and high phosphate load are important contributers to CKD-MBD.

Objectives: This working group has the aim to i) provide education and training for the management of CKD-MBD in children, to ii) perform clinical studies on this topic, and to iii) develop appropriate guidelines.

Activities: We provide educational material on the management of CKD-MBD on the ESPN website, which is regularly updated (Coordinator: J. Bacchetta). We make suggestions for topics and speakers for symposia on CKD-MBD at the annual ESPN meetings.

Educational project (Coordinator: S. Bakkaloglu):

In this project new strategies in *hyperphosphatemia management* are introduced into clinical practice (ESPN research grant *2014.01*). Children with CKD usually take a fixed dose of phosphorus binder. The Phosphate Education Program (PEP) provides simple training tools to instruct patients/parents to eye-estimate meal phosphorus content based on phosphorus units consept and to self-adjust the number of phosphorus binders accordingly. A pilot study using PEP approach showed improved hyperphosphatemia control without reducing phosphorus intake in children. We are currently extending this concept to European pediatric nephrology units. A clinical study is not feasible because of the high financial burden. Therefore, it is planned to prepare detailed educational material which will be distributed to ESPN units. This will include a cell phone application.

Guidelines and recommendations for treatment in children with CKD:

Clinical practice recommendations for vitamin D treatment in children with CKD and on dialysis (Coordinator: R. Shroff). The ESPN CKD-MBD working group and the ESPN Dialysis working group joined together to develop two treatment guidelines on native and active vitamin D treatment in children. A group of 7 group members and a representative of the Methods Support Team of the European Renal Best Practice, as well as a pediatric pharmacist met in Heidelberg in December 2015 and in May 2016 for 1 ½ day.

The manuscript is currently under review in *Nephrol Dial Transplant*. Travel *costs* and accommodation (3800€) was covered by the general ESPN support of the WGs (each 50%) for 2015.

Clinical practice recommendations for growth hormone treatment in children with CKD (Coordinator: D. Haffner). The ESPN CKD-MBD working group and the ESPN Dialysis working group joined together to elaborate treatment guidelines on GH treatment in children. A group of 7 group members, and 2 representatives of the ESPN/ERA-EDTA registry, as well as a pediatric pharmacist met in Heidelberg in November 2016 for 1 ½ day. The first draft of the guideline was made. The ESPN Transplant WG (coordinator B. Tönshoff) has joined us meanwhile for this review. In the next three months the group members will further elaborate the guideline and it is planned that the group will meet again in May 2017 in Heidleberg.

It is planned to submit the guideline to *Pediatric Nephrol* or *Nephrol Dial Transplant* at the end of 2017. Travel *costs* and accommodation (approx. 4300€) will be covered by the general ESPN support of the WGs for 2017.

We are performing *three* **observational studies**:

In the *first* study (coordinator: D. Haffner) we investigate the effects of vitamin D supplementation on bone/mineral metabolism in pediatric CKD patients. The results of this study were presented as a poster at the IPNA meeting in Iguazu (see abstract), and the

manuscript is almost ready for submission to *cJASN*. The *costs* for the assays (11000€) are covered by the ESPN research grant *2014.01.*

Abstract IPNA 2016

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

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Objectives: The effects of vitamin D supplementation (vit. D suppl.) on CKD-MBD (beside PTH levels) are unknown. Here we investigate the effects of vit. D suppl. on biomarkers of CKD-MBD using two pediatric CKD populations, i.e. controlled randomized trial on ergocalciferol (ERGO) suppl. (Shroff, cJASN 2012), and 4C Study cohort.
Methods: 80 vit. D deficient patients (25(OH)D ≤75 nmol/L) started on vit. suppl. or not with CKD II-IV were included. This included 40 pts. from ERGO trial (each n=20), and 20 pts. started on cholecalciferol suppl. and 20 controls without vit. suppl. (matched by age, sex, eGFR, and serum calcium) from 4C. Serum levels of Klotho, intact/c-term FGF23, and sclerostin were assessed at baseline and after a median period of 6 mo. (range 4-12) using age- and sex-related SD scores (SDS). **Results:** Patients from 4C presented with more advanced CKD (eGFR, 24 *vs.* 55 ml/min/1.73m²), were older (mean age 13 *vs.* 9 yrs.), shorter (height SDS, -1.66 *vs.* -0.81), showed higher PTH levels (13 vs. 4 pmol/l) and received phosphate binders more frequently (38 vs. 13%) compared to ERGO pts. (each $p<0.001$). At baseline, median Klotho levels were decreased in ERGO pts. (-0.74 SDS, $p<0.05$), and normal in 4C pts. (-0.20 SDS). FGF23 levels were elevated in 4C pts. (2.28 SDS, $p<0.05$), but normal in ERGO pts. (0.0 SDS). Sclerostin levels increased in 4C pts., but decreased in ERGO pts. (0.57 *vs.* -0.94 SDS, each $p<0.05$). Klotho levels in ERGO pts. (0.1 SDS) were normalized after vit. suppl. and associated with 25(OH)D levels (each $p<0.05$), but unaffected in 4C pts. (0.1 SDS). FGF23 levels in 4C pts. were further stimulated by vit. D suppl. (3.4 SDS, $p<0.05$), but unaffected in ERGO pts. (0.2 SDS). Sclerostin levels were normalized by vit. D in ERGO pts. (-0.1 SDS, $p<0.05$), but unaffected in 4C pts. (0.7 SDS).
Conclusions: Vit. D suppl. normalizes Klotho and sclerostin levels in patients with mild CKD, but further increases FGF23 levels in advanced CKD.

The *second* study (coordinator: R. Shroff) will assess calcium balance in children with chronic kidney disease to optimise treatment strategies (*Cal-Bal study*). We have developed a novel, non-invasive method of assessing Ca balance by natural Ca isotope fractionation testing. Knowing a patient's Ca balance and status of bone turnover allows us to provide safe and effective treatment that prevents Ca deficiency or overload. We will measure Ca balance in children with CKD stage 3-5 and on dialysis and compare with age, gender and pubertal stage matched healthy children. This study is presented by the ESPN CKD-MBD and Dialysis Working Groups and will be conducted across 5 centres in 4 countries: London, Heidelberg, Hannover, Lyon and Athens. We have received an ESPN grant for €15,000 for the project (*2016.02).*

Conclusions: The activities of our working group are expected to improve the prevention and treatment of CKD-MBD associated complications in children and young adults.

Planned activities in 2017:

- Finish GH guidelines by December 2017. We also plan a second meeting of the authors in Heidelberg in May 2017.
- Finish publication on the effects of vitamin D treatment in children with CKD by March 2017. Intended journal: cJASN
- PEP Study: Finish study protocol, ethics committee approval, and organize training of dieticians at the local centres.
- Go on with the Cal-Bal study (inclusion of patients)
- Update of our website with respect to teaching

Dieter Haffner on behalf of the ESPN CKD-MBD working group