CKD-MBD - B

MO007 **TREATMENT OF SECONDARY HYPERPARATHYROIDISM IN THE EVOLVE TRIAL**

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Introduction and Aims: Secondary hyperparathyroidism (HPT) is common in patients on maintenance hemodialysis and often progresses despite treatment with vitamin D sterols and phosphate binders.
Methods: The EVOLVE trial randomized 3883 patients with moderate to severe secondary HPT with a median plasma intact parathyroid hormone (PTH) concentration of 693 pg/mL (normal range 11–72 pg/mL) to treatment with cinacalcet or placebo. The majority of patients also received vitamin D sterols and phosphate binders. Patients were followed for up to 64 months. We assessed the rates of parathyroidectomy (PTX), switching to commercial cinacalcet, and progress to severe unremitting HPT (defined as iPTH values >1000 pg/mL and serum total calcium >2.6 mmol/L on two consecutive occasions, or iPTH > 1000 pg/mL and serum total calcium >2.6 mmol/L on one occasion with prescription of commercial cinacalcet).
Results: In the group randomized to placebo (n=1935) nearly 70% received vitamin D sterols and 90% phosphate binders throughout the trial. Nonetheless, 278 (14.4%) patients had surgical PTX, with a median (p10, p90) iPTH level of 1873 (760, 3706) pg/mL before surgery, 443 (22.9%) patients started commercial cinacalcet with a median iPTH of 1108 (455, 2310) pg/mL, and 470 (24.3%) progressed to severe unremitting HPT with a median PTH of 1510 (810, 2991) pg/mL. Substantial selection bias was evident in patients who either underwent PTX, were prescribed commercial cinacalcet, or progressed to severe unremitting HPT, with these outcomes differing widely by age, sex, region and comorbidity. The unadjusted relative hazard in the cinacalcet vs. placebo group for PTX was 0.44 (95% CI 0.36-0.54), for provision of commercial cinacalcet 0.41 (95% CI 0.35-0.48), and for progression to severe unremitting HPT with hypercalcemia 0.43 (95% CI 0.37-0.50).
Conclusions: Severe unremitting HPT developed frequently in patients randomized to placebo in EVOLVE, despite the use of conventional therapy with vitamin D sterols and phosphate binders, prompting PTX or motivating the off-protocol use of commercial cinacalcet. Randomization to cinacalcet resulted in a nominally significant reduction in the occurrence of these events.

MO008 **COSMOS: ABNORMALITIES IN THE MAIN BONE AND MINERAL BIOCHEMICAL PARAMETERS ARE ASSOCIATED WITH HIGHER RISK OF MORTALITY**

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Introduction and Aims: Chronic kidney disease mineral and bone disorders are important complications of CKD5D patientsand have been reported to be associated with a higher risk of mortality. The objective of this study was to assess the association of serum calcium (Ca), phosphorus (P) and parathyroid hormone (PTH) with mortality in the European COSMOS study.
Methods: COSMOS is a 3-year, multicenter, open-cohort, prospective study carried out in adult chronic hemodialysis (HD) patients from 20 European countries. At baseline and every 6 months, demographics, comorbidities, drug prescription, monthly serum biochemical parameters of the previous six months and clinical outcomes were collected. Mean biochemical parameters of the previous 6 months were calculated and categorized in several categories. Cox' proportional hazard regression with time-dependent covariates was used to study the association between mortality rate and serum Ca, P and PTH. The Hazard Ratios were adjusted (adHR) by for demographics, centre funding (public/private), country, comorbidities, therapies and biochemical parameters (Ca, P, PTH, albumin and haemoglobin).
Results: A total number of 4500 patients were randomly recruited for COSMOS at baseline. During the 3 years of follow-up, 2297 new patients (less than 1 year on HD) were additionally recruited to replace those dying or leaving the study by other reasons (total number of patients 6797). Patients with no follow-up data or lacking information on biochemical parameters were excluded, making a total number of 6295 patients available for the analysis (4313 [68.5%] randomly selected and 1982 [31.5%] replacements). Both, high and low serum P and PTH were significantly associated with a higher risk of mortality, whereas high serum Ca but not low serum Ca was associated with an increased risk of mortality (Table).
Conclusions: In COSMOS, a representative European HD population, abnormalities in serum PTH and P and a higher Ca were associated with a higher risk of mortality. Study supported by Amgen and Fundación Renal Íñigo Álvarez de Toledo.

MO009 **TISSUE CONTENT OF PHOSPHOROUS IN CKD-MBD. IS CKD-MBD A STATE OF TISSUE PHOSPHOROUS DEPLETION?**

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Introduction and Aims: CKD-MBD is considered a state of phosphate loading. It is postulated that in CKD3 renal excretion of phosphate is maintained at the expense of rising serum FGF23, which increases fractional glomerular excretion of phosphate. However, it is not until CKD 4 that elevation of serum phosphate is regularly seen. High levels of FGF23 are associated with adverse outcomes such as progression of CKD and LVF. There is speculation that use of phosphate binders in early CKD3 might result in lower FGF23 levels and a reduction in associated adverse outcomes. Clear evidence for progressive phosphate accumulation with progressive loss of kidney function does not exist; yet studies are already being conducted on the basis of this assumption. However other studies suggest that CKD may not be a state of positive phosphate balance (Munro P et al 2012). Total tissue phosphorous can be measured by simple laboratory techniques. Twenty-three isotopes of phosphorus are known, including all possibilities from P24 up toP46. Only P31 is stable and hence can be measured. We report the results of a pilot study to estimate the phosphorous content in skin biopsy samples from 20 dialysis patients selected for radiological evidence of vascular calcification, and 10 control subjects without CKD.
Methods: Dialysis patients with radiological evidence of vascular calcification, and control subjects without CKD, were invited to take part and give written informed consent. Each subject underwent a forearm skin biopsy under local anaesthetic. Samples were acid-digested and incinerated to measure the tissue content of phosphorous-31. Tissue content of Calcium-43 was also estimated. Serum calcium, phosphate, albumin, alkaline phosphatase and PTH levels were measured.
Results: Mean skin P31 in the biopsy samples from dialysis patients(n=15) was 298mcg/g as compared with 364mcg/g in controls(p=0.23).No correlation was seen between tissue content of phosphorous and serum phosphate, or with serum PTH. A positive correlation was seen between the tissue content of P31 and Ca43.
Conclusions: Our preliminary data show no significant difference in skin phosphate levels between subjects and controls, and do not support the assumption that CKD is a state of tissue phosphate loading, at least in skin. Indeed there is a trend towards lower skin phosphate levels in the dialysis patients with vascular calcification compared to controls. The positive correlation between the tissue levels of Ca43 and P31 suggest that phosphorous in tissue exists in combination with Calcium. Further sample analysis is on-going and will increase the reliability of the preliminary results.

MO008

Serum Ca (mg/dL)	aHR [95% CI]	Serum P (mg/dL)	aHR [95% CI]	Serum PTH (pg/mL)	aHR [95% CI]
<8.5	1.10[0.92-1.31]	<3.0	1.54[1.23-1.94]	<50	1.35[1.10-1.66]
8.5-9.0	1.06[0.90-1.24]	3.0-4.0	1.16[0.99-1.37]	50-150	1.02[0.88-1.19]
9.0-9.5	1 (Reference)	4.0-5.5	1 (Reference)	150-300	1 (Reference)
>9.5	1.36[1.16-1.60]	5.5-6.5	1.38[1.18-1.62]	300-500	0.95[0.79-1.14]
		>6.5	1.51[1.25-1.81]	500-800	0.97[0.76-1.23]
				>800	1.35[1.16-1.60]

MO009

Mean values	Dialysis patients	Controls	P-values (2-sample t-test)
Phosphorous-31	298 mcg/g	364 mcg/g	0.23
Calcium-43	5.5 mcg/g	6.87 mcg/g	0.40

MO010 **THE RELATIONSHIP BETWEEN RENAL OSTEODYSTROPHY AND FIBROBLAST GROWTH FACTOR-23 IN HEMODIALYSIS PATIENTS**

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Introduction and Aims: The studies on the association between fibroblast growth factor-23 (FGF-23) and mineral metabolism disorders occurred in chronic kidney disease together with cardiovascular outcomes aroused interest about the relationship between renal osteodystrophy and FGF-23.In this study, we aimed to investigate the relationship between FGF-23 and renal osteodystrophy assessed by dynamic bone biopsy findings in chronic hemodialysis patients.
Methods: Among the 207 prevalent hemodialysis patients who underwent bone biopsies, plasma intact FGF-23 levels were measured in 180 patients who had plasma samples stored at -80°C.
Results: The mean age of patients in the study group was 57.8 ± 14.4 years. The mean plasma level of FGF-23 was found as 257 ± 387 pg/ml (14.8-1297). FGF-23 levels were positively correlated with serum phosphate levels (r=0.440, p<0.001), serum calcium levels (r=0.294, p<0.001), serum creatinine level (r=0.302, p<0.001) and calcium-phosphate product (r=0.482, p<0.001). While FGF-23 levels were negatively correlated with serum alkaline phosphatase levels (r=-0.231, p=0.003), it was not detected any significant correlation between serum parathyroid hormone levels and FGF-23. Adynamic bone disease and hyperparathyroid-related bone disease were present in 75% and 25% of the patients, respectively. Plasma FGF-23 levels were not significantly different between the two groups. Plasma FGF-23 level was negatively correlated with mineralization lag time (r=-0.233, p=0.009), osteoid surface area (r=-0.183, p=0.01) and osteoid thickness (r=-0.150, p=0.04) (Table 1). However, it was not observed any independent association between these parameters and FGF-23 in adjusted analyses.
Conclusions: Although high FGF-23 levels were associated with improvements in bone mineralization parameters, the lack of an independent relationship was suggested that FGF-23 was not effective alone in the pathogenesis of renal osteodystrophy. Taken into consideration interactions between parameters such as FGF-23, phosphate, calcium, vitamin D and parathyroid hormone, it is envisaged that the pathogenesis of renal osteodystrophy is more complex.

MO011 **INDIVIDUALISATION OF DIALYSATE CALCIUM: INTRADIALYTIC BIOLOGICAL IMPACT**

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Introduction and Aims: It is crucial to determine an optimal dialysate calcium concentration (DCC) in patients on haemodialysis (HD). Although DCC

MO010

	Mean ± Standard Deviation	Univariate association with FGF-23 r	p
Bone Turnover			
Bone formation rate/Bone surface (mm^3/cm^2/year)	1.59 ± 2.22	0.008	0.91
Activation frequency (/year)	0.34 ± 0.44	0.01	0.86
Osteoblast surface/Bone surface (%)	1.76 ± 3.27	-0.07	0.32
Osteoclast surface/Bone surface (%)	1.27 ± 1.37	-0.13	0.06
Mineralization			
Osteoid surface/Bone surface (%)	33.06 ± 20.28	-0.18	0.01
Osteoid thickness (μm)	10.87 ± 4.19	-0.15	0.04
Mineralization lag time (days)	140.97 ± 189.87	-0.23	0.009
Volume			
Bone volume/Tissue volume (%)	1.92 ± 2.31	0.03	0.60
Trabecular thickness (μm)	93.70 ± 27.81	0.03	0.60

individualisation has long been advocated, most dialysis centres use a fixed value: typically 1.25 mmol/L in the USA and 1.5 mmol/L in European countries. We recently reported the mid-term results of an investigation into the intradialysis biological impact of individually targeted DCC values (1). **Aims:** to assess biological changes during dialysis treatments carried out using individual DCC prescriptions. The goal was to maintain normal serum calcium levels and serum parathyroid hormone (PTH) levels between 150 and 300 pg/mL.
Methods: HD patients at a single institution were observed during a mid-week dialysis session. Pre- and postdialysis ionized calcium (iCa), total calcium (tCa), and PTH levels were recorded, along with the medications used. Patients were divided into 4 subgroups according to predialysis iCa quartiles. HD was performed using DCCs of 1.25, 1.5, and 1.75 mmol/L according to our individualisation strategy. Session length varied from 4 to 8 h. Haemodiafiltration (HDF) was used in 30% of the patients.
Results: We analysed 139 patients with a mean age of 71.8 ± 14 years. Of these, 41.6% were female, the mean dialysis duration was 67.8 ± 75 months, and 36.5% had diabetes mellitus. A DCC value of 1.75 mmol/L was used in younger patients, who had higher serum PTH levels and were less likely to have cardiovascular disease. The treatment involved administration of calcium carbonate (20%), calcium acetate (12%), sevelamer (31%), alfacalcidol (17%), cinacalcet (12%), and cholecalciferol (96%). The mean delta iCa values (from pre- to postdialysis) were -0.01 ± 0.06 mmol/L (from predialysis: 1.14 ± 0.07 to postdialysis: 1.13 ± 0.07 mmol/L) with a DCC of 1.25 mmol/L; 0.09 ± 0.08 mmol/L (from 1.13 ± 0.07 to 1.22 ± 0.07 mmol/L) with a DCC of 1.5 mmol/L; and 0.19 ± 0.1 mmol/L (from 1.15 ± 0.08 to 1.35 ± 0.1 mmol/L) with a DCC of 1.75. The delta iCA was dependent on baseline iCa and whether HDF was used, but not dependent on the session time. Delta iCa was correlated with DCC – Pre-iCa (0.37 ± 0.2 mmol/L; -0.06 to +0.8 mmol/L); a neutral iCa balance was maintained with a mean DCC – pre-iCa value of 0.18 mmol/L. Using DCC – tCa, a neutral calcium balance (median value, 2.2 mmol/L) was achieved using a DDC of 1.38 mmol/L (1.3 mmol/L if HDF was used). Delta PTH (%) was correlated with delta iCa (r² = 0.42; p < 0.001).
Conclusions: Using our individualized DDC strategy, a DCC of ≥ 1.5 mmol/L was found to provide a positive intradialytic ionized calcium balance for most patients. This positive balance is larger when HDF is used. The calcium balance is also dependant on predialysis iCa levels and inversely correlated with intradialytic PTH variations. The HD session time does not affect the calcium balance. 1- Jean, G et al, NDT 2012.