Nephrology Dialysis Transplantation 27 (Supplement 2): ii146–ii158, 2012
doi:10.1093/ndt/gfs219

MINERAL AND BONE DISEASE - CKD 1-5

FP218 CLINICAL AND DEMOGRAPHIC PREDICTORS FOR VITAMIN D DEFICIENCY IN MULTI-ETHNIC ASIAN PATIENTS WITH CHRONIC KIDNEY DISEASE

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Introduction and Aims: Vitamin D deficiency is common in patients with chronic kidney disease (CKD) and can result in complications such as mineral and bone disorders. Vitamin D deficiency is also associated with extrarenal and extraskeletal complications. The purpose of this study is to determine the clinical and demographic risk factors for vitamin D deficiency in multiethnic CKD patients in Singapore, a sun-rich country, so that patients at risk for vitamin D deficiency can be identified early, and replacement with vitamin D supplements can be started before further worsening of their kidney function.
Methods: Pre-dialysis CKD patients from the National University Hospital (NUH), Singapore, Outpatient Renal Clinic who had their serum 25-hydroxyvitamin D [25 (OH)D] levels measured between January 2008 and October 2010 were included in the study. The patients' clinical and demographic parameters were collected from hospital databases and medical charts. Data mining methodology was used to identify potential predictors for vitamin D deficiency in these CKD patients. Two models, Mt30 and Mt16, were built using threshold serum 25(OH)D levels of £30 and <16 ng/mL, respectively.
Results: A total of 219 patients were included in the study. Approximately 83% of the patients had serum 25(OH)D levels £30 ng/mL, while 25.6% had serum 25(OH) D levels <16 ng/mL. Four predictors of vitamin D deficiency were identified. Patients not taking vitamin D supplements (ergocalciferol/cholecalciferol), those with type 2 diabetes mellitus or younger in age were more likely to be vitamin D deficient. Malay and Indian race was also associated with vitamin D deficiency. The area under the receiver-operating curve for the validation sets were 0.708 and 0.752 for the Mt30 and Mt16 models, respectively.
Conclusions: Vitamin D deficiency is common among multiethnic CKD patients in Singapore. Risk factors for vitamin D deficiency identified in this study include absence of vitamin D supplementation, presence of diabetes mellitus, younger age, and Malay and Indian race. The knowledge of these risk factors is useful for predicting vitamin D deficiency in CKD patients in Singapore. This can guide healthcare professionals on their decisions to prescribe vitamin D supplements to CKD patients at risk for vitamin D deficiency.

FP219 22-OXACALCITRIOL PREVENTS PROGRESSION OF ENDOTHELIAL DYSFUNCTION THROUGH ANTI-OXIDATIVE EFFECTS IN RATS WITH TYPE 2 DIABETES

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Introduction and Aims: Vitamin D deficiency is associated with endothelial dysfunction in type 2 diabetes patients. However, the beneficial effect of vitamin D has not been fully elucidated. We assessed whether 22-oxacalcitriol (OCT), a vitamin D receptor activator, could prevent endothelial dysfunction in type 2 diabetes mellitus (DM) rats.
Methods: DM rats (blood glucose > 250 mg/dL) were treated for 10 weeks by intraperitoneal administration of OCT (0.2 μg/kg) three times per week or subcutaneously implanted insulin pellet. After the treatment, femoral flow-mediated dilation (FMD) was measured by high-resolution ultrasound, and the expression levels of NADPH oxidase and endothelial nitric oxide synthase (eNOS) in femoral arteries were investigated by western blot analysis. In cultured endothelial cells treated with high glucose (35.6 mM) and OCT (10 nM), reactive oxygen species (ROS) production was measured with fluorescent probes.
Results: Insulin treatment significantly suppressed the decreased FMD in DM rats by normalizing blood glucose levels. OCT significantly improved the lowered FMD at peak vasodilation after reperfusion (DM: 8.3±1.2% vs. OCT: 15.4±2.4%, n=6) without hypercalcemia or hyperphosphatemia, affecting blood glucose or blood pressure. OCT significantly suppressed the elevated p22phox, a subunit of NADPH oxidase, and improved dimer/monomer ratio of eNOS in femoral arteries. In endothelial cells, OCT directly inhibited high glucose-induced ROS generation by suppressing the elevated mRNA of p22phox expression.
Conclusions: In DM rats, OCT improved endothelial dysfunction without inducing hypercalcemia and hyperphosphatemia, and did not decrease blood glucose or suppress blood pressure. The underlying mechanism might be partly due to suppression of ROS generation through improving p22phox expression.

FP220 EFFECT OF VITAMIN D ON VASCULAR LESIONS AND OXIDATIVE STRESS AT EARLY STAGE OF DIABETIC NEPHROPATHY

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Introduction and Aims: Vascular disease is one of the crucial complications in diabetes. A growing body of evidence suggests that oxidative stress play a key role for the progression of vascular disease. Furthermore, recent studies demonstrated a strong link between vitamin D and cardiovascular disease. We investigated the effect of vitamin D on vascular lesions and oxidative stress at early stage of diabetic nephropathy.
Methods: In this study, we used spontaneously diabetic Torii (SDT) rats, which is the model of non- obese type 2 diabetes. At 20 weeks, SDT rats were divided into 3groups: diabetes (DM, n=6), DM + insulin (DM+I, n=6) and DM + 22-oxacalcitriol (DM+D, n=6). The rats were sacrificed at 30 weeks, and we evaluated blood and urine samples, histopathological analysis of aorta and mRNA expression of VCAM-1, ICAM-1, MCP-1 and NADPH oxidase in aorta.
Results: Blood pressure, creatinine clearance and serum calcium and phosphate levels were comparable among 3 groups. Urinary 8-OHdG was significantly lower in the DM+I and DM+D groups than in the DM group. Immunohistochemical analysis demonstrated that the number of 8-OHdG positive cells in aorta was significantly lower in the DM+I and DM+D groups than in the DM group. Furthermore, the mRNA expression of MCP-1, NADPH p22 and NADPH p47 markedly decreased in the DM+I and DM+D groups compared to the DM group.
Conclusions: Our results suggested that vasoprotective effect of vitamin D be mediated by the reduction of oxidative stress in diabetes.

FP221 VITAMIN D RECEPTOR ACTIVATORS PRESERVE VASCULAR CALCIFICATION BY REDUCING OSTEOPROTEGERIN LEVELS IN HEMODIALYSIS PATIENTS

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Introduction and Aims: Vascular calcification is associated with increased mortality and morbidity in hemodialysis patients. Recent studies showed that elevated osteoprotegerin (OPG) levels are associated with vascular calcification, all cause and cardiovascular mortality in hemodialysis patients. This study investigated the effects of vitamin D receptor activators (VDRAs, paricalcitol and calcitriol) treatments on serum OPG levels in hemodialysis patients.
Methods: Thirty-two hemodialysis patients (14 women, 18 men) with secondary hyperparathyroidism in whom PTH level was >200 pg/mL, calcium (Ca) level was <9.5 mg/dL, Phosphorus (P) level was <5.5 mg/dL were included the study. Study patients were randomized 1:1 to receive paricalcitol or calcitriol treatments, and both groups included 16 participants. Patients were allowed to adjust phosphate binders. During the study serum PTH, Ca, P levels were measured monthly. Maximum daily dosage of calcium-containing phosphate binders was 1500 mg. Biochemical and

FP221 Table 1 Results of biochemical tests and OPG levels at baseline and 3th month

	Paricalcitol group (n:16)		Calcitriol group (n: 16)	
	Baseline	3th month	Baseline	3th month
Phosphorus (mg/dL)	4.4±0.4	4.4±0.8	4.7±0.7	4.8±0.9
Calcium (mg/dL)	8.7±0.4	9.0±0.5[a]	8.8±0.5	9.3±0.4[b]
PTH (pg/mL)	549.4±203	292±173[b]	579±277	384±296[a]
OPG (pg/mL)	10.2±5.3	8.4±4.4[b]	8.4±4.7	7.2±4.8[a]

a : $p < 0.05$, b : $p < 0.01$

hematological tests and OPG levels were measured at baseline and 3th month of the study.
Results: There was no significant difference between the groups in terms of demographics and baseline laboratory tests. No difference was found between paricalcitol and calcitriol groups regarding change from baseline and percent change in biochemical markers and OPG levels. When compared to baseline levels significant increase in Ca (p=0.025 vs 0.001) levels and significant decreases in PTH (p=0.001 vs 0.039) and OPG (p=0.001 vs 0.006) levels were noted at 3th month in paricalcitol and calcitriol group, respectively. There was no difference between paricalcitol and calcitriol groups regarding change from baseline levels and percent changes in PTH (-%44 vs. -%32), Ca (%4 vs. %5), P (%0.5 vs. %2), CaxP (%4 vs. % 7) and OPG (-%16 vs. -%15) levels.
Conclusions: Decreasing effect of calcitriol and paricalcitol on OPG levels might be associated with lower cardiovascular mortality rates of patients receiving vitamin D receptor activators. No difference was noted between two therapeutic agents regarding their effects on OPG levels. These findings should be confirmed by further large-scale studies.

FP222 IMPROVED IPTH LOWERING OF PARICALCITOL VS. CINACALCET IN SUBJECTS ON HEMODIALYSIS: ANALYSIS OF THE IMPACT STUDY

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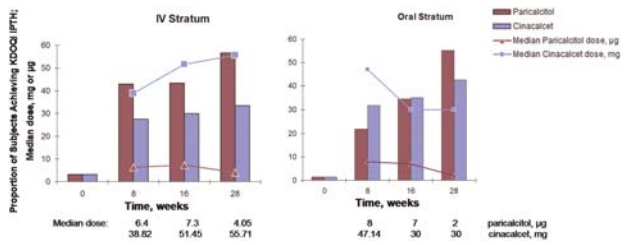
Introduction and Aims: Recently published observational data suggest that hemodialysis patients with KDOQI- defined iPTH target levels may be at lowest risk of mortality when compared to those outside the range suggesting that hemodialysis patients may benefit from SHPT therapies that treat iPTH levels toward the former KDOQI target range. Using data from IMPACT-SHPT, we report achievement of KDOQI-defined iPTH targets over time with paricalcitol in comparison to cinacalcet.
Methods: IMPACT-SHPT was a randomized 28 wk, phase 4, international, open-label study of subjects undergoing hemodialysis receiving IV (IV Stratum) or oral paricalcitol (Oral Stratum), compared with subjects receiving cinacalcet with low-dose vitamin D. An ANOVA model was used to evaluate the comparability of the baseline means between treatment groups within each stratum. Categorical variables were summarized by frequency and percentages and treatment group comparability within each stratum was evaluated using Fisher's exact test.
Results: In the IV Stratum, there were 62 paricalcitol and 64 cinacalcet subjects (60% male, mean age: 61±12 years, mean duration of dialysis:4.1±4.0 years). For the Oral Stratum, there were 72 paricalcitol subjects and 70 cinacalcet subjects (65% male, mean age: 65±13 years, mean duration of dialysis: 3.9±3.2 years). Baseline demographics were similar across treatment groups and strata with the exception of type 2 diabetes, which was significantly more prevalent in the Oral Stratum in the paricalcitol group (p<0.05). In the IV Stratum, the proportion of subjects with left ventricular hypertrophy were greater in the paricalcitol group (p<0.05) and the proportion of subjects with type 1 diabetes was numerically higher, but not statistically significant (p=0.0598). In the IV Stratum, the proportion of subjects achieving KDOQI iPTH levels during weeks 21-28 was significantly greater in the paricalcitol group compared to cinacalcet. In the Oral Stratum this difference was numerically, but not statistically, greater in the paricalcitol group. In the IV and oral strata, a continuously increasing proportion of the subjects achieved KDOQI iPTH levels in weeks 8, 16 and 28, despite the reduction in paricalcitol dose (Figure).
Conclusions: These data show an increasing benefit in control of SHPT with paricalcitol treatment over time, despite decreasing doses, as assessed by the proportion of patients achieving KDOQI guideline-defined iPTH levels. For cinacalcet, however, there was minimal or no increase in the proportion of subjects achieving KDOQI iPTH levels, despite maintenance of a stable dose. This may be of clinical importance since recent observational data have suggested that adherence to iPTH levels close to or within the former KDOQI target range for treatment of patients with CKD are associated with superior outcomes.



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FP223 EFFECTS OF THE SELECTIVE VITAMIN D RECEPTOR (VDR) AGONIST, PARICALCITOL, COMPARED TO CINACALCET ON CALCIUM, PHOSPHORUS AND IPTH: RESULTS FROM THE IMPACT SHPT STUDY

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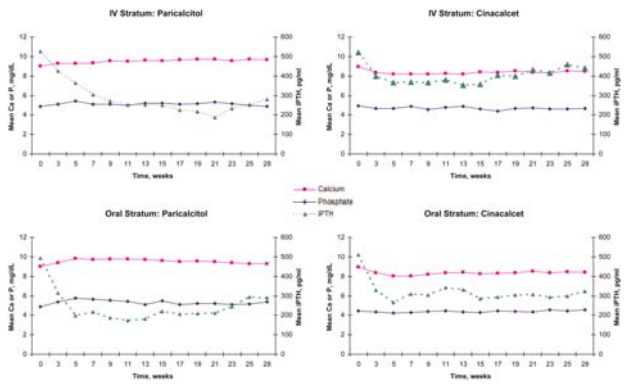
Introduction and Aims: In hemodialysis patients, treatment with vitamin D receptor activators (VDRA) has been associated with reduced cardiovascular and all-cause mortality. However, the use of non- selective VDRAs is associated with an increase in serum calcium, while paricalcitol, a selective VDRA, mitigates these effects while maintaining iPTH lowering benefits. Recently published observational data suggest that hemodialysis patients with iPTH levels in the range of the former KDOQI guideline targets may be at lowest risk of mortality when compared to those outside the range. Here we report results from the IMPACT-SHPT study which compared treatment effects of paricalcitol, a selective VDRA, with cinacalcet plus low dose vitamin D, on calcium, phosphorus and iPTH.
Methods: IMPACT was a randomized 28 wk, phase 4, international, open-label study of subjects undergoing hemodialysis receiving IV (IV Stratum) or oral paricalcitol (Oral Stratum), compared with subjects receiving cinacalcet with low-dose vitamin D. Mean iPTH, calcium and phosphorus levels were determined at baseline and every 2 weeks from Week 3 to Week 25 and at Week 28.
Results: In the IV Stratum, there were 62 paricalcitol and 64 cinacalcet subjects (60% male, mean age: 61 ± 12 years, mean duration of dialysis: 4.1 ± 4.0 years). For the Oral Stratum, there were 72 paricalcitol subjects and 70 cinacalcet subjects (65% male, mean age: 65 ± 13 years, mean duration of dialysis: 3.9 ± 3.2 years). The effects of paricalcitol and cinacalcet on calcium, phosphorous, and iPTH are shown in the figure. In both strata of the study, paricalcitol treated subjects attained KDOQI-defined iPTH targets (150-300 pg/mL) more often when compared with cinacalcet-treated subjects, with relatively constant calcium and phosphorous levels.
Conclusions: Paricalcitol treatment reduces iPTH levels in patients with SHPT, while having minimal effects on calcium and phosphorus levels.



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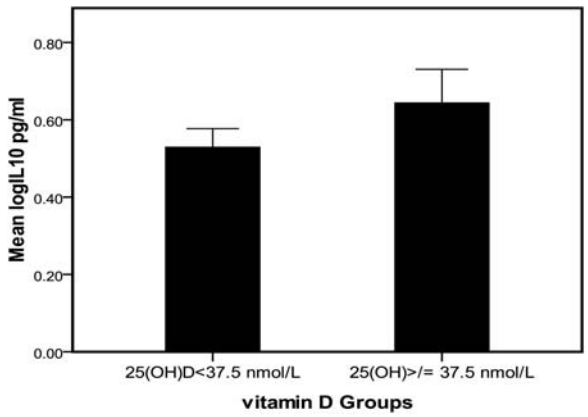

FP224 Figure 1: Serum concentrations of IL-10 in CKD patients with and without severe vitamin D deficiency.

FP224 VITAMIN D IS LINKED WITH ANTI-INFLAMMATORY CYTOKINES IN PATIENTS WITH NON-DIALYSIS DEPENDENT CKD

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Introduction and Aims: Epidemiological studies have identified a direct association between Vitamin D deficiency and chronic inflammation along with a predisposition to autoimmune disease. A chronic inflammatory milieu is a risk factor for cardiovascular (CV) disease and progression of chronic kidney disease (CKD). We examined the association of native and active vitamin D levels on circulating cytokine expression in a pre-dialysis CKD population in this cross-sectional study.
Methods: 114 adult stage 3-5 pre-dialysis ambulant, vitamin D naïve outpatients, not on phosphate binders, were examined in this cross-sectional study. A cytokine 25-plex panel InvitrogenTM Luminex® immunoassay was used for quantitative determination of a series of cytokines and serum signal transduction proteins. Serum 25 hydroxy vitamin D [25(OH)D] and 1,25 dihydroxy vitamin D [1,25(OH)2D] were measured by radioimmunoassay. All non-parametric variables were log10 transformed. Data were analysed using SPSS v.17.
Results: The characteristics of the study population were: age 55±15 years, males 60%, diabetes mellitus 16%, statin therapy 42%, MDRD eGFR 45±23ml/min/1.73m2, Median±IQR serum Fibroblast Growth Factor 23 (FGF-23), PTH & hsCRP concentrations were 65±75 RU/ml, 58±69ng/L and 2.03±3.07mg/L, respectively. Mean±1sd serum 25(OH) D and 1,25(OH)2D concentration were 51±24 nmol/L and 64±39 pmol/L respectively. Serum 1,25 (OH)2D showed a negative correlation with IL-12 (r= -0.291, p=0.002), log10IL- 2R (r= - 0.287, p=0.002), Eotaxin (r= -0.202, p=0.032) whereas, serum 25(OH) vitamin D was negatively correlated with log10IL-8 (r=-0.239, p=0.011) only. Patients with significant 25(OH)D deficiency (25(OH) D<37.5 nmol/L) had a lower log10IL-10 compared to patients with 25(OH)D>37.5 nmol/L (0.52±0.14 vs. 0.64±0.38 pg/ml, p=0.02) (figure 1). On multivariate linear regression analysis, 25(OH)D confirmed an independent effect on log10IL-8 adjusted for eGFR and serum FGF-23 (ad.β= -0.266, p=0.003, 95%CI -0.004 to - 0.001). However, 1,25(OH)2D did not show an independent association with inflammatory cytokines when adjusted for GFR.
Conclusions: 25(OH)D may have an anti-inflammatory effect independent of GFR by inhibiting chemotaxis of polymorphonuclear leucocytes and inhibition of pro-inflammatory cytokines via induction of IL-10. 25(OH)D may, therefore, represent a novel player in the CKD-inflammation-CVD cardio-renal axis.

FP225 CALCITRIOL DIRECTLY INFLUENCES FETUIN-A SYNTHESIS THROUGH ITS ACTION ON HEPATOCYTE VDR

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Introduction and Aims: End-stage renal disease (ESRD) patients are commonly affected by secondary hyperparathyroidism. Treatment with calcitriol reduces serum PTH levels, but may result in an increased risk of vascular calcifications. Vascular calcifications were previously considered as a simply passive process, mainly due to an elevation in serum calcium- phosphate (Ca x P) product levels. However, growing evidence indicates that vascular calcifications are the result of an active process in which several biochemical actors play a role. Fetuin-A, a serum glycoprotein synthesized in human liver tissue, is the prototypic vascular calcification inhibitor, accounting for approximately 50% of the calcification inhibitory capacity of the human plasma. Although the perception about the higher risk of vascular calcification among ESRD patients treated with calcitriol may be well founded, it is difficult to determine whether treatment with calcitriol can directly contribute to vascular calcification or if such vascular pathology is exclusively related to increased Ca x P product levels. Since human hepatocytes express vitamin D receptor and little is known about the effects of calcitriol on fetuin-A synthesis, we performed this study to investigate the effects of calcitriol on fetuin-A expression and release from human hepatocytes.
Methods: Primary human hepatocytes (Gibco Hepatocyte, Invitrogen, U. K.) were cultured according to the manifacturer's protocol. The cells were then stimulated with calcitriol (Calcijex 1 mcg/mL, Abbot, Italy) at 25, 50 and 100 nmol/L for periods of 0, 24, 48 hours. Quantitative RT-PCR analysis of fetuin-A expression and western blotting were performed. A reduction of more than 2-folds in mRNA and protein level was considered significant.
Results: Calcitriol decreased both fetuin-A mRNA expression and protein level in cultured primary human hepatocytes in a time and dose dependent manner. A significant reduction in fetuin-A mRNA expression was observed 48 hours after calcitriol stimulation with a decrease in mRNA level of more than 2 folds when compared to control. Moreover, a reduction of 2.5 folds was also observed for fetuin-A protein synthesis.
Conclusions: Our results show that 1,25-Dihydroxyvitamin D treatment may decrease fetuin-A synthesis through its action on the hepatocyte vitamin D receptor. They identify an additional direct pathologic mechanism for vitamin D-dependent vascular calcification that is completely unrelated to changes in mineral metabolism.

FP226 BODY FAT IS A PREDICTOR OF HYPOVITAMINOSIS D IN RENAL TRANSPLANT PATIENTS.

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Introduction and Aims: Hypovitaminosis D is highly prevalent in the general population worldwide and underlying mechanisms include ageing, skin color, prevention of sunlight exposure and obesity, among others. We aimed to evaluate vitamin D status and the risk factors for hypovitaminosis D among renal transplant recipients in a sunny country like Brazil.
Methods: Serum 25-hydroxy-vitamin D [25(OH)D] was determined in 90 renal transplant patients (58M/32F, 43 10 years old) with serum creatinine <2.0 mg/dL, after 6 months of transplantation (6-165 months interval). Anthropometric and body composition evaluation (bioelectrical impedance), bone densitometry, serum biochemical and hormonal determinations and urinary biochemistry were assessed. Clinical data were obtained from their medical records. Factors associated with hypovitaminosis D were evaluated by using a logistic regression analysis.
Results: Hypovitaminosis D was observed in 58 patients (65%), with levels indicating Insufficiency [25(OH)D < 30 ng/mL] in 53% and Deficiency [25(OH)D < 15 ng/mL] in 11%. When compared to the group with normal 25(OH)D levels, the Hypovitaminosis D group showed a higher % of blood collections obtained during winter (65 vs 29% , p< 0.001), and prevalence of patients under Cyclosporine (CyA) vs Tacrolimus-based immunosuppressive regimens (45 vs 19 % , p<0.05). Hypovitaminosis D group also exhibited higher mean serum PTH (131±79 vs 90±43 pg/ml, p<0.05), body fat (31±10 vs 20±7 %; p<0.001), waist circumference (93±12 vs 86±12 cm, p<0.05) and body mass index, BMI (29±6 vs 25±5 kg/m2, p<0.001). Age, skin color, dialysis vintage, time since transplantation, current renal function, serum albumin, calcium, phosphorus and FGF23 as well as 24-hr urinary calcium, phosphate fractional excretion, albuminuria and % of osteopenia did not differ between groups. Serum 25(OH)D correlated inversely with BMI (r=-0.49, p=0.0001), body fat (r=-0.65, p=0.0001) and waist circumference (r=-0.32, p=0.003). A Logistic Regression Analysis involving all the above parameters revealed that body fat was an independent predictor of Hypovitaminosis D (odds ratio 1.25; 95% CI 1.1-1.4, p< 0.0001), adjusted for collections obtained at either summer or winter.
Conclusions: These findings suggested a high prevalence of 65% of Hypovitaminosis D among renal transplant patients in Brazil and that the percentage of body fat represented the strongest predictive factor associated with this condition, corrected for seasonal variation.

FP227 IS A 25 VITAMIN D DEFICIENCY A RISK FACTOR FOR ANEMIA IN CHRONIC KIDNEY DISEASE PATIENTS?

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FP227 Table 1 Anemia Prevalence according to 25 VD level

	25VD < 15pg/ml	25VD≥15pg/ml	P
	50%	20.5%	0.000
All			
Diabetics	45.7%	15.4%	<0.05
Non Diabetics	57.1%	23.1%	<0.05
CKD stage 4-5	63.2%	24.1%	0.000
CKD stage 3	22.2%	10.0	0.3

Introduction and Aims: Low levels of 25 Vitamin D (25VD) have been described in the general population and in chronic kidney disease (CKD) patients (Pts). CKD Pts with 25VD deficiency has been found to have higher mortality and End Stage Renal Disease rates. The action of 25VD exceeds mineral metabolism and has also been related to the reduction of inflammatory state. The objective of this study is to evaluate the prevalence of severe 25VD deficiency and its association with anemia in CKD Pts stages 3-5 (not on dialysis).
Methods: Cross sectional study. 25VD levels were measured in CKD pts stages 3 to 5 (not on dialysis) and considered severely deficient if lower than 15 ng/ml. Pts with 25VD severe deficiency (25 VD-SD) were compared to those without it regarding: age, gender, diabetic status, GFR, calcium, phosphorus, hemoglobin, ferritin, iPTH bicarbonate and alkaline phosphatase levels. Anemia was defined as an hemoglobin level <11 g/l. Anemia and 25 VD-SD were analyzed/stratified by diabetic status and CKD stage. Comparisons were made with t test or chi square as needed. All p values were two-tailed; $p < 0.05$ was considered significant. Risk for anemia was analyzed with a multivariable logistic regression.
Results: One hundred and forty Pts were studied at the CKD clinic, 74 males (52.9%) mean age 62.9±16.1 years, 64 diabetics (45.7%). CKD stage III in 38 (27.1%), IV in 78 (55.7%) and V not on dialysis in 24 (17.1%). 25VD levels were lower than 30ng/ml in 76.5 % of Pts and 54 (42.6%) had 25VD-SD. There were not statistical differences in age, GFR, Proteinuria, Calcium, phosphorus, iPTH or bicarbonate levels between Pts with or without 25VD-SD. Vitamin D deficit was more frequent in females (51.5%) than males (34.4%), and in diabetics 62.1% vs 38.3% non diabetics. Anemia frequency was 32.8 % and increased with advanced CKD stage. Patients with 25 VD-SD had significantly lower Hb levels f (11.1±1.6 vs 12.2±1.7) Half of the pts with severe 25VD deficit had Hb < 11g/l vs 20.5%, even stratifying to diabetic status and CKD stage 25VD deficient Pts had lower Hb levels (Table I). In subjects with 25 VD-SD compared with subjects without 25 VD-SD, OR for anemia controlling for age, gender, diabetic status, and CKD stage was 4.76 (95% CI 2-04–11.23).
Conclusions: Severe Vitamin D deficit is frequent in CKD Pts. since early CKD stages, and more prevalent in diabetic and female patients. A low hemoglobin level is associated to 25 VD severe deficiency. Studies are needed to evaluate the effect on the hemoglobin of the treatment with 25 VD deficits levels. The action of VD on the reduction of inflammation could be a pathway to explain this relationship

FP228 THE EFFECT OF CHOLECALCIFEROL SUPPLEMENTATION IN CHRONIC KIDNEY DISEASE

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Introduction and Aims: Over last decade, interest in vitamin D it has become increasingly, due to its high prevalence of deficiency in general population and in chronic kidney disease (CKD) patients.
Methods: We performed a observational study of 25(OH) Vitamin D levels of a sample comprising 751 incident patients referred to our outpatients clinic (mean age 67.2 [±15] years, mean GFR [MDRD-4] 47.9 ±25. 5 ml/min/1.73m2, 59.3% males, 32.1% diabetics). Secondly, we studied the characteristics of the patients with 25 (OH) vitamin D deficiency (<15 µg/L). Finally, we studied the effect of low doses Cholecalciferol supplementation (400 U/day) in this population.
Results: Only 10% of our patients had adequate 25 (OH) vitamin D levels (> 30 µg/L). Mean 25 (OH) vitamin D levels was 17,1 (± 13) µg/L. Elderly people ($p=0.0002$), female gender ($p=0.02$), and diabetes ($p=0.03$) were closely associated with 25 (OH) vitamin D deficiency. 25 (OH) Vitamin D deficiency was inversely associated with serum PTH ($p= 0.02$), and directly associated with serum calcium ($p<0.0002$). Patients under RAS (renin-angiotensin- aldosterone system) inhibitors or Allopurinol treatment presented significantly lower 25 (OH) vitamin D levels in multivariate analysis ($p= 0.011$ and $p=0.013$ respectively), however patients with Statins treatment had lower vitamin D level ($p= 0.029$). Supplemented patients with low dose of Cholecalciferol presented a significant increase in 25 (OH) vitamin D levels ($p< 0.001$), and also significant decrease in concentrations of C-reactive protein (CRP) ($p=0.036$).
Conclusions: 25 (OH) D deficiency has a high prevalence in CKD patients, and the severity of this deficiency increases with the progression of kidney disease. Elderly, women and diabetic patients have a higher risk of Vitamin D deficiency. Some treatments with anti-inflammatory effect like RAS inhibitors or Allopurinol could increase 25(OH) Vitamin D level. However the effect of statins treatment in 25(OH) vitamin D level is unclear. Low dose Cholecalciferol supplementation is safe and effective treatment, and could produce significantly effects in inflammatory markers.

FP229 THE EFFECT OF ORAL VITAMIN D SUPPLEMENTATION IN CKD PATIENTS

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Introduction and Aims: The anti-inflammatory, antifibrotic, and antiproteinuric properties of vitamin D have been defined in studies using active vitamin D analogs. Here, we evaluate the effects of nutritional vitamin D supplementation on bone mineral metabolism and progression of renal disease in CKD patients.
Methods: We conducted randomized controlled trial in adult, vitamin D deficient [25(OH) D < 30 ng/mL], non-dialytic CKD patients. The patients were randomized to receive either oral vitamin D supplementation (cholecalciferol 1000 IU/day) or not for 6 months. The serum level of 25(OH) D, parathyroid hormone (PTH), calcium, phosphate, alkaline phosphatase, creatinine, and urinary protein excretion were measured serially.
Results: Ninety seven patients were enrolled (vitamin D group, n = 49; control group, n = 48). The baseline characteristics were not different between vitamin D group vs. control group. Vit D supplementation achieved the improvement in serum 25(OH) D level (vitamin D vs. control, 28.01 ± 12.82 ng/mL vs. 13.50 ± 7.29 at 3 month, p <0.001; 29.49 ± 16.19 vs. 14.17 ± 8.17 at 6 month, p < 0.001). This difference was persistent in the subgroup analysis of baseline GFR <30 mL/min/1.73m2 vs. GFR 30-60 or 25(OH) D <15 ng/mL vs. 25(OH) D 15-30. PTH level was decreased in the vitamin D group compared to control group (vitamin D vs. control; 40.2 (26.8 – 72.0) pg/mL vs. 54.2 (38.2 – 101.1) at 3 month, p = 0.013; 38.8 (19.2 – 65.3) vs. 58.1 (39.5 – 137.0) at 6 month, p = 0.014). Vitamin D supplementation increased corrected calcium level compared to control at 3 month, whereas the difference was not significant at 6 month. The level of phosphate, estimated GFR, and random urine protein-to-creatinine ratio were not different. During the study period, four patients in vitamin D group and five in control group started renal replacement therapy. The most common adverse effects related with oral vitamin D therapy was gastrointestinal irritation. There was no case of symptomatic hypercalcemia.
Conclusions: Oral vitamin D supplementation was effective in replenishing vitamin D store in CKD patients. However, we could not find any beneficial effect on renal disease progression.

FP230 FIVE YEARS FOLLOW UP OF 25 OH VITAMIN D REMPLACEMENT THERAPY IN 165 CANADIAN DIALYSIS PATIENTS WITH CHOLECALCIFEROL 10000 UNITS ONCE A WEEK.

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Introduction and Aims: Low serum 25OH D vitamin concentration (25OH D) is a frequent finding in dialysis patients and may exacerbate bone change associated with hyperparathyroidism, osteoporosis, osteomalacia and the risk of fracture. Others effects of 25OH D deficiency have been correlated to increased risk of cancer, immunodeficiency, increased cardiovascular risk and cardiovascular death, muscle weakness, cognitive impairment, infection and anemia. We previously reported correction of 25OH D deficiency/insufficiency after 6 months . Even though 25OH D is increasingly prescribed to hemodialysis patients there is limited data on the safety and long term effects of once a week cholecalciferol supplementation in a dialysis cohort.
Methods: Prior to April 2007, 25OH D deficiency / insufficiency in our dialysis patients was not treated and there was a very high prevalence of deficiency. We undertook replacement therapy with cholecalciferol 10000 units (D Tabs) administered once a week by the dialysis nurse assuring 100% compliance and corrected the deficiency over a 6 months period. We continued supplementation

until December 2011. Calcium, phosphorus, PTH , alkaline phosphatase, magnesium, total protein, albumin, and hemoglobin were measured. ESA dose, phosphate binder and active vitamin D were documented. 25OH D was measured yearly on October, November and December. Search for episodes of hypercalcemia and other side effects were documented

Results: After 5 years of treatment, paired data for 25OH D was available for 68 patients. There was a yearly increased of 16.49 nmol/L (p=0.0001). The number of patients in the cohort decreased according to mortality, transplant and transfer to other dialysis facilities. 25OH D dosages for most patients reached a plateau despite constant administration. There was no significant change in the use of ESA, phosphate binders and active vitamin D. In October, November and December 2011, 0 patient had a severe deficiency (<12nmol/L) 0 patient had mild deficiency (12-39 nmol/L) 6 patients (6.6%) had insufficiency (40-75 nmol/L) 38 patients (55.9%) had adequate levels (>75nmol/L) 22 patients (32.3%) had elevated levels (>150 nmol/L) and 2 patients (2.9%) had toxic levels (>250nmol/L)

Conclusions: 25OH D deficiency/insufficiency was successfully and safely corrected in our dialysis population. Target 25OH D levels were maintained for 5 years with once a week supplementation of cholecalciferol 10000 units without adverse events. This data confirms that using oral cholecalciferol 10000 units once a week is a safe and adequate dose that could be considered for other large prospective trial in this population.

FP231 UREMIA SUPPRESSES IMMUNE SIGNAL-INDUCED CYP27B1 EXPRESSION IN HUMAN MONOCYTES, WHILE INCREASING BACKGROUND EXPRESSION.

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Introduction and Aims: Local production of 1,25(OH)2D regulated by the CYP27B1 enzyme in monocytes contributes to the immunomodulatory effects of vitamin D. Uremia suppresses renal CYP27B1 but its impact on monocytic CYP27B1 is incompletely understood. We investigated the contribution of 2 uremic toxins on uremic modulation of monocytic CYP27B1 expression.

Methods: Resting or immune (interferon-? + lipopolysaccharide)-stimulated THP1 cells and human monocytes, isolated from healthy donors, were cultured in the presence of either healthy or uremic serum, or p-cresyl sulfate (PCS) or indoxyl sulfate (IndS), after which RNA expression levels for CYP27B1 and cytokines were quantified by qRT-PCR.

Results: Culturing THP1 cells or human monocytes in the presence of uremic serum led to higher inflammatory cytokine and CYP27B1 expression. Immune-signal induced CYP27B1 expression however was impaired in the presence of uremic serum (2-fold; p=0.01). No effect of either PCS or IndS was demonstrated on CYP27B1 regulation in THP1 cells or human monocytes due to their unability of these toxins to enter monocytes.

Conclusions: Monocytic baseline CYP27B1 expression is increased in uremia, probably reflecting the micro-inflammatory state. Immune signal-induced CYP27B1 expression, conversely, is impaired in uremic conditions. PCS and IndS do not contribute to this dysregulation as they cannot enter monocytes. Dysfunctional monocytic vitamin D metabolism may contribute to the high cardiovascular and infectious burden in chronic kidney disease.

FP232 1,25D/25D RATIO TO ASSESS THE OVERALL BALANCE OF VITAMIN D HYDROXYLASES (OH-ASE).

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Introduction and Aims: The overall balance resulting from the activities of the enzymes involved with vitamin D synthesis and degradation, can be regarded as determinant of circulating 1,25D levels and of sensitivity to replacement therapies. In fact, in different clinical conditions, anabolic and/or catabolic enzymes are differently regulated by stimulating or inhibiting hormones, thus resulting in variable 1,25D levels. Moreover we can anticipate that cases with more efficient overall OH-ases activity are less dependent from available cholecalciferol stores, and more sensitive to replacement therapies. In this study we hypothesized that the ratio between the active hormone, 1,25D, and its most significant precursor, 25D, could represent an indirect tool to estimate the overall balance of OH-ases activity.

Methods: We evaluated this parameter in two CKD populations, CRF on conservative therapy and renal TX patients, who presumably are developing or, respectively, recovering from secondary hyperparathyroidism. Thus the overall OH-ase activity is expected to be different. The two CKD populations (70 CRF and 80 TX), were naïve to vitamin D therapy and selected to be comparable for age (58 ±15 vs. 54±10 y) (M±SD), renal function (eGRF 45±22 vs. 46±15 ml/min) and 25D levels (23±11 vs. 26±11 ng/ml). As control, we considered 300 subjects with normal renal function (N; age 45±14 y; eGFR 113±14 ml/min; 25D 25±13 ng/ml).

Results: 1,25D levels were 24±13, 42±15 and 50±16 pg/ml respectively in CRF, TX and N (p<.001). The ratio 1,25D/25D was 1,4±1,05 in CRF, 2.0±1,4 in TX, and 3.0 ±2,4 in N (p<.0001). To evaluate the influence of Vitamin D stores, we considered the ratio separately in cases with 25D=20 ng/ml (0.9±0.5 in CRF; 1.4±0.6 in TX and 2.0±0.5 in N; p<.0001) and in those with 25D<20 ng/ml (2.2±1.2 in CRF; 3.4±1.6 in TX and 4.0±3.3 in N; p<.001). In each group the ratio was significantly different between the two storage conditions (p<.001). Further, the ratio correlated negatively with 25D in each population (p<.0001), but r values increased definitely moving from linear to non-linear models in N (from 0.556 to 0.774) and in TX (from 0.692 to 0.812), but not in CRF (from 0.648 to 0.692). This last finding suggests an exponential increment of efficiency along with vitamin D depletion only in two of the populations considered.

Conclusions: Our data indicate that the ratio 1,25D/25D, as expected in feed-back biologic systems, is negatively correlated with the available substrate and shows the highest values in case of deficiency. Moreover CRF patients experience the lowest values, while TX patients show a tendency toward normalization. We suggest that 1,25D/25D ratio could be useful to estimate the overall OH-ase activity and thus to guess sensitivity to replacement therapy.

FP233 IMPACT OF 1,25-DIHYDROXYVITAMIN D ON RENAL FUNCTION IN CHRONIC KIDNEY DISEASE PATIENTS

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Introduction and Aims: Vitamin D deficiency is highly prevalent in patients with chronic kidney disease (CKD). The clinical significance of vitamin D deficiency is emphasized by experimental and epidemiologic data indicating that vitamin D deficiency may contribute to impaired kidney function. The recent data suggested that low 25-hydroxyvitamin D (25(OH)D) levels may be risk factor of end state-renal disease (ESRD). However, the role of 1,25-dihydroxyvitamin D(1,25(OH)2D)in the prevention of kidney disease remains unclear. The aim of this study was to investigate the prognostic value of 1,25(OH)2D level in relationship to deterioration of renal function for CKD stage 3-5.

Methods: Sixty-six CKD patients (33 men, mean age 65.0 ± 11.1; CKD stage 3 (%), 4 (%), and 5) were allocated for study. We divided 3 groups, deficient (1,25(OH)2D <20 pg/mL), insufficient (20 pg/mL =1,25(OH)2D <30 pg/mL), or sufficient (30 pg/mL=1,25(OH)2D), according to serum 1,25(OH)2D levels.

Results: When compared with 1,25(OH)2D deficient groups, CKD patients with sufficient 1,25(OH)2D level had significant higher body-mass index (BMI, 23.5 ± 3.1 vs 26.4 ± 4.0 Kg/m2, p<0.05) and 25(OH)D levels (18.8 ± 13.8 vs 32.6 ± 17.1 ng/mL, p<0.05). There were no significant differences in other baseline characteristics among 3 groups. We evaluated the associations between serum 1,25(OH)2D level and age, BMI, hemoglobin, total protein, albumin, HDL- cholesterol, and spot urine protein to creatinine ratio. Multiple linear regression analysis revealed that patient's BMI and spot urine protein to creatinine ratio were associated with serum 1,25(OH)2D level. The mean renal event-free survival in 1,25(OH)2D deficient, insufficient, and sufficient groups was 11.3 ± 1.8, 13.9 ± 1.5, and 16.3 ± 1.3 months, respectively (log-rank p<0.05). The most common cause of ESRD was progression of underlying renal disease.

Conclusions: These finding suggested that low 1,25(OH)2D levels may be an independent predictor of further development of ESRD in CKD patients. Whether preventing an decrease in 1,25(OH)2D levels reduces the incidence of ESRD must be clarified by prospective follow-up studies.

FP234 PLASMA EXCHANGE INDUCES VITAMIN D DEFICIENCY

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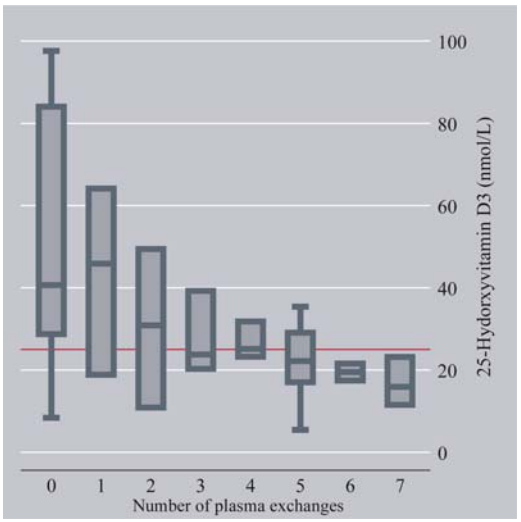
Introduction and Aims: Plasma exchange is a widely used for treating diseases mediated by antibodies or pathogenic proteins, or for transplant desensitisation. However, results from randomised trials of PEX in nephrology have been equivocal. Vitamin D deficiency is associated with skeletal and extra-skeletal pathology, is permissive to activity of a number of autoimmune diseases, and may be associated with poorer renal allograft survival. We asked whether plasma exchange (PEX) would induce vitamin D deficiency through its removal with the 56kDa vitamin D binding protein (DBP).

Methods: We performed a single-centre prospective cohort study of 11 patients receiving plasma exchange at Addenbrooke's Hospital, Cambridge. Vitamin D metabolites, binding protein and biochemical parameters were measured before the start and after every plasma exchange treatment, as well as 7 and 28 days after completion of PEX.

Results: 11 Caucasian European patients (7 males) aged 59 ± 13 years received 5.5 ± 0.9 PEX treatments during the study period, for ANCA-associated vasculitis (n=5),



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myasthenia gravis (n=3), paraneoplastic neuropathy (n=2) and voltage-gated potassium channel antibody-mediated encephalopathy (n=1). Baseline eGFR was 56.9 ± 39.5 ml/min/1.73m2, and 5 patients had CKD3 or worse. Baseline 25 (OH)-vitamin D3 levels were 50.6 ± 30.1 nmol/L. PEX significantly reduced vitamin D levels after 5 treatments to 22 ± 9.4nmol/L (p = 0.0017), and vitamin D remained low 7 days (26.4 ± 9.8nmol/L, p=0.02) and 28 days (30.8 ± 15.5, p=0.048) after cessation of PEX. PEX also significantly reduced DBP levels from 206.5 ± 64.7µg/mL to 98.5 ± 34µg/mL (p = 0.0001). However, in contrast to 25-hydroxyvitamin D3 levels, DBP recovered rapidly, to levels similar to baseline after 7 (194 ± 47.8µg/mL, p=0.63) and 28 days (223.5 ± 69.9µg/mL, p=0.85). PEX significantly reduced corrected Calcium from 2.23 ± 0.12 mmol/L to 1.98 ± 0.08 mmol/L (p = 0.0007), but did not alter phosphate. Analyses of plasma effluent confirmed removal of DBP, vitamin D and PTH by PEX.
Conclusions: We identified for the first time significant and sustained reductions in 25-hydroxyvitamin D3 levels by a typical course of PEX, likely through its removal in the plasma effluent, bound to DBP. Given the mounting evidence of a role for vitamin D in immune modulation, the use of concomitant treatments such as glucocorticoids that adversely affects bone health, and the morbidity associated with its deficiency, vitamin D represents an important therapeutic target for maximising the benefits of PEX, reducing morbidity and improving outcomes. Prospective studies should evaluate vitamin D supplementation in patients receiving PEX. Reference line represents threshold for vitamin D deficiency.

FP235 VITAMIN D DEFICIENCY IN FABRY DISEASE

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Introduction and Aims: Patients with Fabry disease frequently develop left ventricular (LV) hypertrophy and renal fibrosis. Due to heat intolerance and inability to sweat, patients tend to avoid sunlight exposure. We hypothesized that subsequent vitamin D deficiency may contribute to hypertrophic cardiomyopathy (HCM). This study investigated the vitamin D status and its association with LV mass, HCM and adverse clinical symptoms in patients with Fabry disease.
Methods: 25-hydroxyvitamin D (25[OH]D) was measured in 111 patients with genetically proven Fabry disease. LV mass and HCM were assessed by echocardiography and magnetic resonance imaging. In cross-sectional analyses, associations with adverse clinical outcomes were determined by linear and binary logistic regression analyses, respectively, and adjusted for age and sex.
Results: Patients had a mean age of 40±13 years (42% male), and mean 25(OH)D of 23.5±11.4 ng/ml. Those with severe vitamin D deficiency (25[OH]D = 10ng/ml) had an adjusted 10fold higher risk of HCM compared to those with sufficient 25(OH)D levels >30ng/ml (p=0.005). The mean LV mass was meaningfully different with 170 ±75 g in severely deficient, 154±60 g in deficient and 128±58 g in Vitamin D sufficient patients, respectively (p=0.013). With the severity of vitamin D deficiency, the median levels of proteinuria increased, as did the prevalences of depression, edema, cornea verticillata and the need for medical pain therapy.
Conclusions: Vitamin D deficiency was strongly associated with HCM and higher left ventricular mass in patients with Fabry disease as well as adverse clinical symptoms. Whether vitamin D supplementation improves complications of Fabry disease, requires randomized controlled trials.

FP236 TREATMENT OF EXPERIMENTAL RENAL OSTEODYSTROPHY WITH RISEDRONATE

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INTRODUCTION: The use of bisphosphonate for osteoporosis with renal dysfunction has been controversial. Risedronate (Ris) dosing effect on markers of bone turnover, bone mineral density (BMD), and mechanical stiffness in rat 5/6 nephrectomized (Nx) model was unclear.
Methods: Two third of left kidney of ten weeks old male Sprague-Dawley rats was nephrectomized and subsequently right kidney was removed at the age of eleventh weeks. Ris was dissolved in 0.9% saline and was subcutaneously injected for Ris group. Sham operation (Sham) was performed and vehicle was injected for Sham group. Administration of Ris was initiated 4 weeks after completion of nephrectomy. All animals were fed a commercial chow containing 1.0 % calcium and 1.0% phosphorus. Blood sample was collected from inferior vena cava and bilateral femurs were removed. BMD was measured with pQCT and bone stiffness (BF) was quantified with anteroposterior three point bending.
Results: Serum levels of TRAP5b, osteocalcin (OC), and intact PTH (iPTH) in Nx were increased compared with Sham. BMD in cancellous and cortical bone at metaphysis were similar between Nx and Sham. On the other hand, BMD in cortical bone at diaphysis in Nx was diminished and a decrease in BF in Nx was also observed. Weekly administration of Ris 70 or 500 (µg/kg body weight) for a total of 8 weeks decreased serum level of TRAP5b in a dose dependent manner, but did not change serum levels OC and iPTH. Ris 70 and 500 increased total BMD (tBMD) at metaphysic and did not affect tBMD at diphysis in Nx and Sham. Ris 70 increased BMD in cortical bone at diaphysis in Nx. Ris 70 augmented BF in Nx and Sham. Although the effect of Ris 500 on BF was similar to that of Ris 70 in Nx, Ris 500 reduced BF in Sham.
Conclusions: Based on these results, the optimal dose of Ris improves bone fragility counteracting diaphyseal cortical bone resorption in Nx. In addition, the excessive suppression of bone turnover by Ris overdosing varies at different bone sties and depends on presence or absence of renal dysfunction.

FP237 ORAL NITROGEN-CONTAINING BISPHOSPHONATES USE IN TREATMENT OF MINERAL AND BONE DISORDERS (MBD) OF PATIENTS WITH CHRONIC KIDNEY DISEASE (CKD) STAGES 3 AND 4

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Introduction and Aims: Both low bone mineral density (BMD) and hypercalcemia associated with cardiovascular morbidity and mortality in patients with CKD. Defect of mineralization due to high resorption rate often accompanies moderate hyperparathyroidism (mixed form of MBD-CKD) and leads to hypercalcemia and low BMD. Bisphosphonates are used extensively as antiresorptive drugs in general osteoporotic population. Experience of bisphosphonates use in patients with advanced CKD is limited and controversial, but there are several reports confirming its beneficial influence on bone fracture risk and aortal calcification. Aims of our study were to investigate changes of BMD and laboratory parameters of bone metabolism in CKD stages 3 and 4 patients treated with bisphosphonates and to evaluate its safety for these patients.
Methods: 30 predialysis CKD patients (9 M and 21 F, age 57±13,1 years) with mean eGFR 27,1±8,2 ml/min (by Cockcroft & Gault) were selected for this study. Eligibility criteria include low BMD, high resorption rate (estimated by β-cross-laps), serum calcium (sCa) level > 2,5 mmol/l. The patients were administered peroral alendronate 70 mg/week (22) or ibandronate 1500mg/month (8) during 12 mo. BMD at the

FP237 Table 1

Parameters	Baseline	6 months	12 months
BMD lumbar spine (T score)	-2,87±0,98	-2,25±0,67•	-1,89±0,92•
BMD femoral neck (T score)	-2,33±0,76	-2,05±0,45•	-1,94±0,88•
iPTH (pg/ml)	108±24	123±27•	156±35•
sCa (mmol/l)	2,63±0,16	2,44±0,15•	2,35±0,28•
β-cross-laps (ng/ml)	1,328±0,556	1,025±0,486•	0,435±0,248•

- p<0,05

lumbar spine, femur and radius (by DXA) and bone mineral metabolism parameters were measured on baseline and every 6 mo. The progression of aortic/valvular calcification was estimated by echocardiography and lateral abdominal X-ray performed on baseline and after 12 mo of treatment.
Results: Three patients were excluded from the study for upper gastrointestinal irritation during first 2 mo. Remaining 27 patients completed the study without any adverse events. All patients had osteoporosis/osteopenia in all measured regions of skeleton. Valvular calcification presented in 67% of the patient and abdominal aortal calcification – in 39%. Table 1 lists the differences between baseline, 6 mo and 12 mo values of mentioned parameters. Mean BMD increased significantly inversely proportional to decreasing of sCa level. There was a significant but not critical increase in iPTH level. Contemporary β-cross- laps dropped to normal range towards the end of observation. There were no statistically significant differences between baseline and final values of bone-GLA-protein (BGP), serum phosphate (sPi) and alkaline phosphatase (ALP). eGFR had trend to improve. The patients showed no progression of aortal or valvular calcification all over the study.
Conclusions: The time-limited use of oral nitrogen-containing bisphosphonates in selected CKD stage 3 and 4 patients with markedly increased bone resorption and low BMD showed beneficial effects of this treatment on bone turnover (decreasing resorption without reduction of bone formation). It allowed to normalize serum calcium and increase BMD. There were no signs of vascular calcification progression or deterioration of eGFR. In general oral nitrogen- containing bisphosphonates were well-tolerated and demonstrated no serious adverse events.

FP238 IS ALKALINE PHOSPHATASE A USEFUL TOOL FOR CHRONIC KIDNEY DISEASE - MINERAL AND BONE DISORDER ASSESSMENT IN NON-DIALYSIS PATIENTS?

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Introduction and Aims: Elevated serum total alkaline phosphatase (AP) was recently shown as a predictor of cardiovascular morbidity and mortality in chronic kidney disease (CKD), but scarce data from non-dialysis patients yet exist. Hence, we studied the prevalence of increased serum AP and its correlations in stage 2 to 5 non-dialysis CKD patients as compared to non-CKD controls.
Methods: This multicentric, cross-sectional study prospectively enrolled 115 stable non-dialysis CKD patients (61% male; 61 [49-71] years; 8% - stage 2, 49% - stage 3, 29% - stage 4, 14% - stage 5) and 33 patients without CKD, matched for age, gender, tobacco/alcohol use and diabetes mellitus. Subjects with active hepato-biliary diseases, neoplasia or Paget's bone disease were excluded. Biochemical parameters of mineral metabolism (25-hydroxyvitamin D - 25OHD, intact parathyroid hormone - iPTH, phosphate - PO4, calcium - tCa and AP) were measured.
Results: A trend to gradually higher prevalence of elevated AP (>135UI/L, according to the upper laboratory reference limit) with the decline in glomerular filtration rate (GFR) was found (from 0% in non-CKD and stage 2 to 7.1%, 11.8% and 18.8% in stages 3, 4 and 5 CKD, respectively) (p=0.14). Moreover, increasingly AP levels were seen along CKD stages (p=0.04). Serum iPTH and PO4 had similar rises (p<0.001 for each), while 25OHD and tCa showed only slight trend to decrease (p=0.11 and 0.29, respectively) (Table).
In CKD group, a negative correlation between GFR and serum AP was recorded (r= –0.26, p=0.001). In addition, serum AP correlated directly with serum iPTH (r=0.29, p=0.002) and serum phosphate (r=0.29, p=0.001), but inversely with tCa (r= –0.20, p=0.003).
Conclusions: In non-dialysis CKD patients without liver diseases, serum AP increases as kidney function worsens, in close relationship with the main other biochemical parameters of mineral metabolism. Thus, it seems reasonable to include AP in the assessment plan for mineral and bone disorder, because AP could be a useful, non-invasive, marker of potential high-turnover bone disease due to secondary hyperparathyroidism, at least in patients with GFR below 30mL/min/1.73m2.

FP238 Table 1

Parameter	Non-CKD group (n=33)	CKD group Stage 2 (n=9)	Stage 3 (n=56)	Stage 4 (n=34)	Stage 5 (n=16)
Serum AP (IU/L)*	71 [67-84]	67 [51-80]	76 [64-105]	94.5 [68-112]^{a,b}	107 [68-124]^{a,b,c}
Serum iPTH (pg/mL)*	56 [36.8-75]	47.6 [45-81]	71.6 [49-102]^{a}	165 [69-265]^{a,b,c}	416 [233-464]^{a,b,c,d}
Serum 25OHD (ng/mL)*	13.8 [10-20.3]	19.4 [12.8-21.8]	13.4 [8.6-19.4]	12.5 [8.4-17.5]^{a,b}	11.9 [8.2-15]^{b}
Serum PO4 (mg/dL)#	3.3±0.5	3.3±0.6	3.3±0.6	4.2±0.9^{a,b,c}	5.0±1.5^{a,b,c,d}
Serum tCa (mg/dL)#	9.6±0.6	9.7±0.6	9.6±0.6	9.4±0.7	9.0±1.3^{c}

* Median [interquartile range]; # Mean ± SD; p<0.05: a vs. non-CKD group; b vs. stage 2; c vs. stage 3; d vs. stage 4

FP239 ARE MINERAL METABOLISM ABNORMALITIES PREDICTORS OF VASCULAR CALCIFICATIONS IN NON-DIALYSIS CHRONIC KIDNEY DISEASE?

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Introduction and Aims: Vascular calcifications, due to traditional and non-traditional risk factors (including mineral metabolism abnormalities), are highly prevalent in chronic kidney disease (CKD) patients. Although lumbar aortic calcification score (ACS) provides a simple and inexpensive method to evaluate vascular disease, little is known about its determinants in pre-dialysis stages of CKD. Thus, we aimed to assess ACS relationships with certain uremia-related factors in adults with or without CKD.
Methods: A prospective, cross-sectional, single-center study on 106 stable patients with non-dialysis CKD (60% male; 62 [51-72] years, 55% over 60 year-old; 49% - stage 3, 35% - stage 4, 16%- stage 5) and 34 age- and gender-matched patients without CKD (47% male; 59 [46-66] years, 50% over 60 year-old) was conducted. Only 4% of CKD subjects were treated with calcium salt and none with vitamin D derivatives. Medical history and blood pressure measurement were obtained. Abdominal aortic calcification score was evaluated according to Kauppila on a plain lateral lumbar X-ray. Automatic waveform analyzer measurements and carotid artery ultrasonography were performed to assess the cardio-ankle vascular index (CAVI), ankle-brachial index (ABI) and carotid intimae-media thickness (IMT). Some non-traditional risk factors (serum calcium - tCa, phosphate - PO4, intact parathyroid hormone - iPTH, 25 hydroxy-vitamin D - 25OHD, C-reactive protein - CRP) and serum albumin (sAlb) were measured.
Results: The proportions of patients with diabetes mellitus, obesity, and active smoking were similar (26% in CKD group vs. 18% in controls, p=0.35, 32% vs. 26%, p=0.54, and 13% vs. 18%, p=0.71, respectively). Higher ACS was found in CKD (1 [0-5.8]) vs. non-CKD patients (0 [0-1]), p=0.003, especially in those with stages 4 (4 [1-7]), p<0.001, and 5 (7 [3-11]), p<0.001. Univariate linear regression showed strong positive associations of ACS with CKD duration (rs=0.32, p<0.001), PO4 (r=0.26, p=0.002), iPTH (rs=0.35, p<0.001), and CRP (rs=0.32, p<0.001), while glomerular filtration rate (GFR, rs=–0.50, p<0.001), sAlb (r=–0.18, p=0.04) and gender (r=–0.18, p=0.04) were inversely associated. No relationships with age, 25OHD, IMT, and indices of arterial stiffness (CAVI, ABI) were found. However, in a model of multiple linear regression that accounts for 30% of ACS variation (p<0.001), only GFR (t ratio=2.55, p=0.01), tCa (t ratio=2.57, p=0.01) and male gender (t ratio=2.15, p=0.04) were independent predictors of the aortic calcification score.
Conclusions: Abdominal aortic calcifications are more prevalent in non-dialysis CKD patients as compared to their Control counterparts matched for the main traditional cardiovascular risk factors. In adults with and without CKD, lower GFR and higher serum calcium are determinants of ACS. Thus, the decline of kidney function below 30mL/min/1.73m2 appears as an independent risk factor for vascular calcifications. Among mineral metabolism parameters, only calcium burden seems involved.

FP240 INCREASED SERUM PHOSPHATE CONCENTRATIONS IN PATIENTS WITH CHRONIC KIDNEY DISEASE TREATED WITH DIURETICS

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Introduction and Aims: Hyperphosphatemia occurs quite late in the course of chronic kidney disease (CKD). In addition to the severity of CKD and dietary phosphate load, other factors may be involved in determining serum phosphate levels. Diuretics can alter mineral metabolism in patients with CKD, and they may increase serum phosphate levels. The aims of this study were to determine the prevalence of hyperphosphatemia in a cohort of CKD patients not yet on dialysis, and to ascertain whether diuretic therapy is associated with increased serum phosphate levels.
Methods: Cross-sectional study in 922 Caucasian patients (65±15 years, 430 females) with a GFR < 40 ml/min (mean GFR 14.3±4.9 ml/min), not treated with phosphate binders or vitamin D. Sixty- three percent of patients were on diuretics. By multiple linear and logistic regression analyses, the determinants of serum phosphate levels (continuous variable) and hyperphosphatemia (serum phosphate > 4.5 mg/dl) were assessed. Diuretic treatment was included in the models together with other independent variables of interest.
Results: Mean serum phosphate levels were 4.79±1.12 mg/dl, and 512 patients had serum phosphate levels >4.5 mg/dl (55%). Compared with the rest of the study patients, those treated with diuretics had significantly higher mean serum phosphate levels (4.88±1.08 vs. 4.65±1.16 mg/dl; 95 % C.I. of the difference = 0.38 to 0.08 mg/dl, p= 0.002). Diuretic treatment was shown to be associated with serum phosphate levels (beta = 0.093; p=0.001), and with prevalent hyperphosphatemia (OR 1.72; C.

I.95% 1.25 – 2.28; p=0.001), in models adjusted for age, sex, GFR, protein catabolic rate, serum calcium, bicarbonate, albumin, PTH, proteinuria, and diabetes.
Conclusions: Diuretic treatment is associated with increased serum phosphate levels in patients with CKD. Diuretics should be taken into consideration as potential confounders in the relationship between serum phosphate or phosphatonins levels and cardiovascular outcomes.

FP241 COMPLIANCE WITH KDOQI AND KDIGO GUIDELINES FOR SERUM PHOSPHORUS AND SERUM CALCIUM IN RELATION TO DISEASE PROGRESSION IN PRE-DIALYSIS PATIENTS

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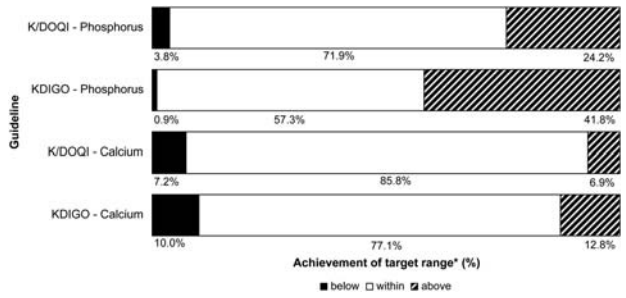
Introduction and Aims: Disturbances of the mineral metabolism are associated with an increased mortality risk in (pre-)dialysis patients. The aim of this study was first to study the association between serum phosphorus and serum calcium levels at the start of pre-dialysis care and a) dialysis free- survival and b) the rate of decline of renal function within the first year of pre-dialysis care. Second, to study whether non-compliance with the KDOQI and KDIGO guidelines for phosphorus and calcium levels is associated with a shorter dialysis-free survival and a faster rate of decline of renal function.
Methods: This study included incident pre-dialysis patients from the prospective PREPARE-2 cohort. Cox regression analysis, adjusted for age, sex, and primary kidney disease, was used to assess the risk (hazard ratio, HR) for the start of dialysis associated with each 0.1 mmol/L increase in phosphorus and calcium level. Linear mixed models adjusted for age, sex, and primary kidney disease, were used to estimate the rate of decline of renal function.
Results: Baseline characteristics: n=426, 68% male, age 65±14 years, eGFR 16.7±6.5 mL/min/1.73m2, phosphorus 1.42±0.32 mmol/L, calcium 2.32±0.15 mmol/L. The percentage compliance with the guidelines for phosphorus and calcium levels is shown in the figure.
Each 0.1 mmol/L increase in phosphorus level was associated with a shorter dialysis-free survival (HR 1.22; 95% CI 1.17 to 1.28), while each 0.1 mmol/L increase in calcium level was not (HR 1.03; 95% CI 0.93 to 1.14). Phosphorus levels below the KDOQI target range were not associated with a shorter dialysis-free survival (HR 0.50; 95% CI 0.14 to 1.78), as compared to patients who complied with the guideline. Due to the small group size, risks associated with phosphorus levels below the KDIGO target range could not be estimated. Phosphorus levels above the target ranges were associated with a shorter dialysis-free survival as compared to levels within the target range (HR 1.86; 95% CI 1.35 to 2.56 and HR 2.56; 95% CI 1.88 to 3.47 with regards to the KDOQI and KDIGO guidelines, respectively). Calcium levels below the KDOQI and KDIGO target ranges were not associated with the duration of dialysis-free survival (HR 0.92; 95% CI 0.50 to 1.67 and HR 1.05; 95% CI 0.64 to 1.72, respectively). For calcium levels above the target ranges the HRs associated with the duration of dialysis-free survival were 1.33; 95% CI 0.75 to 2.34 and 1.37; 95% CI 0.89 to 2.12 for the KDOQI and KDIGO guidelines, respectively. Each 0.1 mmol/L increase in phosphorus level accelerated the mean rate of decline of renal function with -0.91 mL/min/1.73m2/year; 95% CI -1.12 to -0.70. Each 0.1 mmol/L increase in calcium level did not change the mean rate of decline of renal function (-0.39 mL/min/1.73m2/year; 95% CI -0.85 to 0.08). In patients who were non-compliant with the KDOQI and KDIGO target ranges for phosphorus the yearly decline of renal function was comparable with the decline in compliant patients. Similarly, no association between non- compliance for calcium levels and decline of renal function was found.
Conclusions: The present analyses showed that increased phosphorus levels were associated with a shorter dialysis-free survival and a faster rate of decline of renal function within the first year of pre- dialysis care. These results may indicate that successful management of mineral metabolism in pre-dialysis patients is beneficial in postponing the start of dialysis and in decreasing the rate of decline of renal function.



FP241

FP242 Table 1 Incidence of AEs in diabetic and nondiabetic patients

		Low-dose PA21 (1.25 g/day) n (%)	Medium-dose PA21 (5.0 or 7.5 g/day) n (%)	High-dose PA21 (10.0 or 12.5 g/day) n (%)	Sevelamer (4.8 g/day) n (%)
Overall AEs	Diabetic	4 (50.0)	10 (62.5)	14 (82.4)	5 (50.0)
	Nondiabetic	9 (50.0)	19 (54.3)	21 (65.6)	8 (50.0)
GI AEs	Diabetic	0 (0.0)	6 (37.5)	6 (35.3)	3 (30.0)
	Nondiabetic	4 (22.2)	6 (17.1)	7 (21.9)	3 (18.8)
GI AEs excluding discolored faeces	Diabetic	0 (0.0)	4 (25.0)	2 (11.8)	3 (30.0)
	Nondiabetic	2 (11.1)	5 (14.3)	5 (15.6)	3 (18.8)

* Patients with missing information for cause of CKD (17%) excluded

FP242 PA21: AN EFFECTIVE AND WELL TOLERATED IRON-BASED PHOSPHATE BINDER FOR HEAMODIALYSIS PATIENTS, INCLUDING THOSE WITH DIABETES

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Introduction and Aims: Diabetes is a leading cause of CKD, accounting for up to 46% of incident haemodialysis patients. Hyperphosphatemia represents a therapeutic challenge in these patients given the limited choice of effective and well tolerated treatments, particularly because of gastrointestinal (GI) adverse events (AEs). The purpose of the present post-hoc analysis was to investigate the impact of diabetes on the therapeutic response and side effects of the novel iron-based phosphate binder PA21.
Methods: Post-hoc analysis of a randomized, active-controlled, multicentre, open-label, dose-ranging, phase 2 study investigating PA21 vs sevelamer HCl in 152 haemodialysis patients (51 diabetic; 101 nondiabetic). Patients received a fixed-dose regimen of PA21 (1.25, 5.0, 7.5, 10.0 or 12.5 g/day) or sevelamer (4.8 g/day) for 6 weeks. The primary efficacy endpoint was change in serum phosphorus level from baseline.
Results: PA21 reduced serum phosphorus levels in a dose-dependent manner in the overall study population. The efficacy of medium-dose PA21 (5.0 and 7.5 g/day) was similar to sevelamer (4.8 g/day), while high-dose PA21 (10.0 and 12.5 g/day) showed greater efficacy. Of importance, no significant difference in efficacy was observed for diabetic versus non- diabetic patients. All PA21 doses were well tolerated. Except for hypophosphatemia (serum phosphorus <1.13 mmol/L), no dose-dependent association between PA21 and the occurrence of AEs was observed (Table 1). The overall incidence of GI AEs was similar across medium and high- dose PA21 and sevelamer in diabetic patients. No GI AEs were observed in diabetic patients receiving low-dose PA21 (1.25 g/day). The overall incidence of GI AEs was lower in nondiabetic patients, but remained similar across all doses of PA21 and sevelamer (Table 1). The most common GI AE associated with PA21 was discolored faeces, due to the iron. When discolored faeces were excluded, the GI AE profile for PA21 was more favourable than for sevelamer in diabetic and nondiabetic patients. These findings reflect those observed for the overall study population.
Conclusions: These data indicate that PA21 is an effective and well tolerated phosphate binder with a potentially more favorable GI AE profile than sevelamer, when discolored faeces are excluded. Therefore, PA21 is a valuable alternative to current hyperphosphatemia treatments for haemodialysis patients, including those with diabetes.

FP243 MAGNESIUM PREVENTS PHOSPHATE-INDUCED CALCIFICATION IN PRIMARY HUMAN AORTIC VASCULAR SMOOTH MUSCLE CELLS (HAVSMC)

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Introduction and Aims: Vascular calcification is prevalent in patients suffering from chronic kidney disease (CKD). Factors promoting calcification include abnormalities in mineral metabolism, particularly high phosphate levels. Inorganic phosphate (Pi) is a classical inducer of in vitro vascular calcification. Recently, an inverse

relationship between serum magnesium concentrations and Vascular Calcification has been reported. The present study aimed to investigate the effects of magnesium on Pi-induced vascular calcification at the cellular level using primary HAVSMC.
Methods: HAVSMC were obtained from aorta of various donors (ethical procedure approval # 2009/19). Alive as well as fixed HAVSMC were assessed during 14 days in presence of Pi with increasing concentrations of magnesium (Mg) chloride. Mineralization was measured using quantification of calcium, Von Kossa and alizarin red stainings. Cell viability was also assessed using adequate tests.
Results: Co-incubation with Mg significantly decreased Pi-induced vascular calcification in living HAVSMC. Total Mg concentrations of 1.5 or 2 mM in the cell culture media were the most potent ones in terms of preventing the calcification process. No effect was found in fixed cells suggesting that alive cells are necessary for Mg to exert its protective effect. At above concentrations, magnesium also significantly improved cell viability in presence of Pi.
Conclusions: The addition of Mg chloride to a high-phosphate environment significantly reduced vascular calcification in primary HAVSMC. This seems to be an active cellular phenomenon, since the protective role of Mg takes effect only in live, not fixed cells, and concomitantly improves HAVSMC viability. Further investigations are currently ongoing and will shed light on the cellular mechanism(s) by which Mg is able to prevent vascular calcification.

FP244 METABOLIC BONE DISEASE, ATHEROSCLEROSIS AND FIBROBLAST GROWTH FACTOR-23 IN PERITONEAL DIALYSIS PATIENTS

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Introduction and Aims: We aimed to investigate the cardiovascular findings in terms of fibroblast growth factor-23 (FGF-23), fetuin-A, bone mineral metabolism and atherosclerosis in peritoneal dialysis (PD) patients with high and low-turnover bone disease..
Methods: Forty-one PD patients that were followed up between January-June 2010 were enrolled in this study. Demographic findings, etiology of chronic renal failure, time on dialysis, physical examination and treatments were obtained retrospectively. Kt/V urea was calculated to determine PD treatment adequacy. Serum albumin, uric acid, LDL and HDL-cholesterol, triglyceride, CRP and Hb levels were measured. In terms of bone mineral metabolism, age, gender, amount used per day of vit D and elemental Ca, serum Ca, P, iPTH, FGF-23 and fetuin-A levels were determined. Direct hand X-rays (soft tissue and vascular calcification, and the presence of cysts), carotid Doppler ultrasound (intima-media thickness and vascular calcified plaque), echocardiography (valvular calcification, left ventricular hypertrophy, ejection fraction) and eye examination (conjunctival and corneal calcification) were performed. Patients according to levels of iPTH were divided into 2 groups as follows: high- turnover (>300 pg/ml) and low- turnover (= 300 pg/ml) bone disease. Mann-Whitney-U, Pearson's chi-square and Fisher's exact tests were used for statistical analysis.
Results: High and low-turnover bone disease groups did not differ significantly in terms of FGF-23 and fetuin-A levels. P and Ca x P levels in high-turnover bone disease group were significantly higher than the values found in low-turnover bone disease group. Carotid artery intima-media thickness and the number of patients who had calcified plaque on carotid artery in low-turnover bone disease group were significantly higher than high-turnover bone disease group (Table).
Conclusions: PD patients with high and low-turnover bone disease did not differ significantly in terms of FGF-23 and fetuin-A levels. Low-turnover bone disease group was found more risky in terms of atherosclerosis. Table. FGF-23, Fetuin-A, bone mineral metabolism and cardiovascular findings in high and low turnover bone disease.

FP244 Table 1

	High turnover bone disease (n=31)	Low turnover bone disease (n=10)	p
Age (years)	46.1 ± 14.9	51.6 ± 12.8	0.32
Female / Male	24 / 7	8 / 2	0.86
Diabetic / non-diabetic	4 / 27	3 / 7	0.21
Time on dialysis (months)	68.9 ± 40.3	74.4 ± 51.7	0.98
Dose of active vit D (µg / day)	1.5 ± 0.8	0	-
Dose of elemental Ca (mg / day)	1250.0 ± 1412.7	650.0 ± 444.0	0.35
BMI (kg / m²)	25.4 ± 5.1	26.9 ± 5.9	0.34
Kt/V urea (weekly)	1.9 ± 0.2	1.9 ± 0.1	0.85
FGF-23 (RU / ml)	2962.1 ± 2396.2	2064.7 ± 2041.2	0.30
Fetuin-A (ng / ml)	448.4 ± 109.9	390.0 ± 106.8	0.23
Ca (mg / dL)	9.0 ± 0.7	8.5 ± 0.7	0.12
P (mg / dL)	5.3 ± 1.1	4.2 ± 1.1	0.04
Ca x P (mg² / dL²)	48.0 ± 9.2	38.9 ± 10.7	0.01
iPTH (pg / mL)	627.0 ± 445.1	128.0 ± 90.0	-
Hb (g / dL)	10.9 ± 1.3	11.0 ± 1.5	0.89
CRP (mg / dL)	17.2 ± 26.8	8.4 ± 5.8	0.64
Albumin (g / dL)	3.04 ± 0.52	3.03 ± 0.50	0.97
Uric acid (mg / dL)	5.2 ± 0.7	5.4 ± 1.1	0.67
LDL-cholesterol(mg / dL)	101.4 ± 35.6	109.4 ± 43.7	0.84
HDL-cholesterol(mg / dL)	42.8 ± 10.9	39.5 ± 10.3	0.46
Triglyceride (mg / dL)	144.9 ± 70.4	126.4 ± 41.9	0.63
Calcification on hand X-ray	12	2	0.27
Bone cysts on hand X-ray	7	6	0.06
Conjunctival and corneal calcification	26	9	0.54
Calcified plaque on carotid artery	12	8	0.02
Valvular calcification	28	9	0.68
Ejection fraction (%)	54.1 ± 11.0	55.7 ± 9.6	0.79
Left ventricular hypertrophy	10	5	0.31
Carotid intima-media thickness (mm)	0.69 ± 0.14	0.82 ± 0.21	0.03

FP245 EXPRESSION OF FGF23/KLOTHO SYSTEM IN HUMAN VASCULAR TISSUE

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Introduction and Aims: Fibroblast growth factor (FGF)-23 is a recently discovered phosphatonin, produced primarily in bone, whose main action is related to the induction of phosphaturia and inhibition of synthesis of vitamin D. Actions of FGF23 occurs through binding to its receptors (FGFRs), but requires the presence of a cofactor, Klotho, to produce the receptor activation. Thus, only tissues expressing Klotho are targets for the action of FGF23. In addition to effects on mineral metabolism, elevated levels of FGF23 have been associated with increased mortality in patients undergoing hemodialysis. Moreover, increased concentrations of this molecule have been also demonstrated as an independent factor related to raised mortality in the general population. Most of the studies on FGF23-klotho axis have been developed in vitro or in animal models, mainly in organs related to mineral metabolism, and only a few of them have focused on the potential role of FGF23-Klotho system in the human vascular biology. The aim of this study was to characterize the expression of components of the FGF23-Klotho system in human vascular tissue.
Methods: Thoracic aorta samples were obtained from of 104 patients (73 men and 31 women) undergoing elective cardiac surgery (coronary artery bypass surgery and replacement valvular surgery) to determine the tissue-specific expression of FGF23, their cognate receptors and KLOTHO, by using PCR amplification techniques.
Results: Results obtained showed the absence of FGF23 expression in all samples, whereas PCRs of KLOTHO as well as two of the three FGFRs (FGFR1 and FGFR3) generated products of the expected size in all samples. Identity of these fragments was subsequently confirmed by sequencing. Finally, the analysis by real-time PCR confirmed the absence of FGF23 mRNA, while KLOTHO expression it was detected in all samples (117.37 ± 626,02 arbitrary units), demonstrating the constitutive expression of this gene in the human vascular wall. Analysis of differential expression of KLOTHO based on patients' characteristics showed a higher significant expression level in patients with atherosclerotic coronary lesions determined by the coronariographic study. KLOTHO can also function as a humoral factor by membrane proteolytic activity of the enzyme ADAM-17, which releases the soluble form of the protein, whereas a protective activity against endothelial dysfunction by

stimulating the synthesis interleukin-10 (IL-10) has been postulated. Gene expression quantification by real time-PCR of ADAM-17 (5,37 ± 15,26 au) and IL-10 (23,06 ± 80.11 au), showed a direct correlation with the expression levels of KLOTHO: r = 0.57 (p <0.01) and r = 0.51 (p <0.01), respectively.
Conclusions: Our data demonstrate for the first time the existence of the FGF23-Klotho axis in human vascular tissue, suggesting that the vascular wall could be a target for FGF-23 action and that this hormone may play a role in the pathophysiology of cardiovascular disease. Further studies are needed to demonstrate the functionality of the system in this tissue and define the possible mechanisms involved in these effects.

FP246 SERUM FGF-23 IS LINKED WITH INCREASED INFLAMMATORY CYTOKINES IN CKD STAGE 3-5- IS THIS THE EXPLANATION FOR ITS ADVERSE CV EFFECTS?

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Introduction and Aims: Serum Fibroblast Growth Factor 23 (FGF-23) is classically considered a phosphaturic hormone secreted by osteocytes mitigating the effects of secondary hyperparathyroidism and strongly suppressing 1,25 dihydroxy vitamin D (1,25(OH)2D) production. It is closely associated with CV morbidity and mortality in patients with kidney disease having recently been shown to promote LVH. However FGF-23 may have additional adverse CV effects, so to explore this we investigated the link between FGF-23 and chronic inflammation and immunity, known to be a powerful predictors of CV outcomes in CKD. To do this, we measured FGF-23 alongside circulating markers of chronic inflammation in CKD patients, including Interleukin (IL)-12, monokine induced by INF-? (MIG) and IL-8.
Methods: 114 adult stage 3-5 pre-dialysis healthy, ambulant, vitamin D naïve outpatients, not on phosphate binders, were examined in this cross-sectional study. A cytokine 25-plex panel InvitrogenTM Luminex® immunoassay was used for quantitative determination of a series of cytokines and serum signal transduction proteins. Serum FGF-23 was measured by two-site ELISA detecting both C-terminal and intact fragments. All non-parametric variables were log10 transformed. Data were analysed using SPSS v.17.
Results: The characteristics of the study population were: age 55±15 years, males 60%, MDRD eGFR 45±23ml/min/1.73m2. Median ± IQR FGF-23, PTH & hsCRP concentrations were 65±75 RU/ml, 58±69ng/L and 2.03±3.07mg/L respectively. Mean ±1sd serum 25 hydroxy vitamin D and 1,25(OH)2D concentration were 51±24 nmol/L and 64±39 pmol/L respectively. FGF-23 showed a positive correlation with IL-12 (r=0.249, p=0.008), log10MIG (r=0.241, p=0.01), log10 IL8 (r=0.304, p=0.001) and log10 hsCRP (r=0.304, p=0.001). On multivariate regression modelling adjusted for eGFR and 1,25(OH)2D, FGF-23 showed an independent effect on log10 IL-8 (ad.β=0.299, p=0.002, 95%CI 0.00-0.001), log10 MIG (ad.β=0.199, p=0.03, 95% CI 0.00-0.001), hsCRP (ad.β=0.328, p=0.001, 95% CI 0.00-0.002) and IL-12 (ad.β=0.179, p=0.050, 95% CI 0.00-0.07).
Conclusions: FGF-23 is associated with serum levels of pro-inflammatory cytokines, independently of its effect on Vitamin D. This argues that FGF-23 is immunologically active and involved in the heightened CV risk associated with CKD and ESRD. These immunological effects of FGF-23 should be tested in vitro and in a large scale epidemiological study.

FP247 PTH: WHAT ARE WE MEASURING? CLINICAL IMPLICATIONS OF A THIRD GENERATION ASSAY FOR THE DETERMINATION OF PTH LEVELS.

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FP247 Table 1

	Normal	CKD nonHD	HD	PHPT
Number of patients	70	46	105	29
Liaison® (wPTH)	24.7 ± 11	85 ± 93	158 ± 108	174 ± 153
Immulite® (iPTH)	58.1 ± 32	224 ± 213	373 ± 240	376 ± 300
Modular® (iPTH)	43.4 ± 17	188 ± 206	288 ± 180	280 ± 217
Liaison/Modular	0.56 ± 0.7	0.56 ± 0.9	0.54 ± 0.11	0.6 ± 0.16
Liaison/Immulite	0.47 ± 0.13	0.37 ± 0.8	0.44 ± 0.12	0.47 ± 0.15

Introduction and Aims: In the last years, problems related to PTH dosage have been raised. Yet, many nephrologists neither know which method their laboratories are using nor if any change in determination of PTH has occurred. Due to great biological variability and heterogeneity of circulating PTHs, different assays based on different epitopes are being used. PTH levels can thereby change, with the risk of over or underestimation. Clinical implications are important, since PTH levels are crucial in therapeutic decision-making. Second generation PTH assays, largely used in the last decades, are nowadays questioned, because they measure the intact PTH (iPTH), including the N-truncated fragments (supposed to be biologically inactive). Recently a third generation method has been introduced, which is claimed to only measure the whole molecule (wPTH that is 1-84 PTH). We compared this third generation method with two currently available second generation ones in a large cohort of patients.
Methods: We tested 250 patients - 70 normal subjects, 46 patients with renal failure not on dialysis (CKD nonHD), 105 patients on haemodialysis (HD), 29 with primary hyperparathyroidism (PHPT) - with the new third generation assay Liaison® and compared it with the two second generation Immulite® and Modular®. A panel of pertinent parameters, including 25OH vitamin D levels, was also performed.
Results: The table lists mean values and confirms large differences among these, with ratios Liaison/Immulite and Liaison/Modular ranging 0.4-0.6, independently of the group.
There was a close correlation among the three methods: r2 Liaison vs Immulite 0.903, r2 Liaison vs Modular 0.922, r2 Modular vs Immulite 0.941. Concerning normal individuals, low levels of calcifediol partly explained abnormally high PTH levels. This confirms the opportunity to take into account vitamin D status in this contest. The above dependence appeared less important in other groups of patients.
Conclusions: the Liaison assay exhibits good reliability in the assessment of PTH function with good correlation with previous iPTH assays. Mean values of the wPTH measured by Liaison assays are 40 to 60% those of iPTH assays. This must be carefully considered in the management of patients and demandes a close cooperation between clinics and laboratory.

FP248 TOTAL SERUM CALCIUM CORRECTION FORMULAS IN HYPOALBUMINEMIA: WHICH WORKS BETTER?

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Introduction and Aims: Accurate evaluation of mineral and bone metabolism is crucial in the management of patients with chronic kidney disease. International guidelines recommend that serum calcium (Ca) levels be regularly checked in such patients, preferring measurement of ionized Ca (iCa) to that of total Ca (tCa) concentration. Nevertheless, in current practice, tCa measurement is still largely adopted, because this technique is time-sparing, less expensive and more reproducible than that of iCa. Since hypoalbuminemia may lead to a wide range of variations in tCa level, a number of equations have been provided to correct tCa for albumin concentration. We performed this study to determine the value of these equations in estimating the actual concentration of iCa.
Methods: Equations from the literature were selected for study if they included a correction for serum albumin and have been previously validated on patients' data. The equations originally described by Orrell (O), Clase et al. (C), Payne et al. (P) and Jain-Bhayana et al. (JB) met these criteria. We analysed the respective performances of these formulas in 272 consecutive patients with low serum albumin levels (<4 g/dL). Results were then used to estimate the corresponding iCa levels, assuming 50% of tCa be ionized. Correlation, bias, precision and accuracy within 10% of the true serum iCa concentration were determined. Pearson's test was used for correlation, Z-statistics for comparison among correlation coefficients, mean difference between measured and estimated iCa to determine the bias and SD of this mean difference to assess precision. McNemar test and Bland-Altman plots were used to determine accuracy.
Results: Mean measured iCa was 1.12+0.17 mM. The calculated iCa of the O, C, P, and JB formulas were 1.10+0.17, 1.09+0.17, 1.13+0.17, 1.09+0.18 mM, respectively. Estimated iCa correlated well with true iCa for any of the 4 equations. The regression coefficients were similar (0.94; 0.94; 0.93; 0.96; respectively) and did not differ significantly. Nevertheless, the results of the equations differed at least significantly from true iCa and from one another. P equation overestimated iCa level ($p<0.01$), but its bias was significantly smaller in comparison to any other formula. Precision was not significantly different for the majority of formulas with the better results for P equation. Accuracy within 10% for JB formula was significantly lower ($p<0.001$) in comparison with that of the other equations, while the P formula showed a significantly better result ($p<0.01$). Accuracy for O, C, P, JB formulas was 85.4%, 84.3%, 88.6% and 75.7%, respectively.
Conclusions: P formula is the most popular equation used to correct tCa levels. Although this formula overestimated true iCa concentration, the difference was small and of no clinical value. In comparison with other less commonly used equations, P equation seems to improve the estimation of iCa levels in the setting of hypoalbuminemia, because of a similar correlation with measured iCa, smaller bias and greater accuracy.

FP249 PREVALENCE AND PROGRESSION OF AORTIC VASCULAR CALCIFICATIONS IN CHRONIC KIDNEY DESEASE STAGE II, III AND IV.

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Introduction and Aims: The association between vascular calcifications, cardiovascular risk factors, and impaired bone mineral metabolism (MBD) in Chronic Kidney Disease stage 5(CKD-5) is well known. However, little is known on the prevalence and progression of cardiovascular calcifications in the early and intermediate stages of chronic kidney disease (CKD stage 2-3-4). In this cross-sectional study prevalence and degree of aortic vascular calcification (AVC) have been assessed in patients with CKD stage 2-3-4 using the Kauppila index (KI) defined on lateral view of Rx abdomen.
Methods: All patients with CKD stage 2-3-4 seen in our outpatient clinic between March and December 2011 were studied. The IK was calculated on a Rx abdomen in lateral view, in all patients (pts). Other variables recorded were: age, diabetes mellitus, smoking, presence of peripheral vascular disease (PVD), ischemic heart disease (IHD), serum calcium (Ca, mg/dl), serum phosphorus (P, mg/dl), intact serum parathyroid hormone (PTHi; pg/ml), 25OHVitD3 (ng/ml).
Results: 115 patients (76 males), mean age 73.4±9.2 years, were evaluated; 13 (11%) CKD2, 72 (63%) CKD3, 30 (26%) CKD4. Forty five pts (39%) had diabetes (7% in CKD2, 62% in CKD3, 31% in CKD4). 33 pts (29%) had PVD (6% in CKD2, 67% in CKD3, 24% in CKD4). 29 pts (25%) had IHD (7% in CKD2, 59% in CKD3, 34% in CKD4). The average values of serum Ca, P, and PTHi were respectively: 9.4±0.68 mg/dl, 3.5±0.58 mg/dl, 132±94.4 pg/ml with no difference among the three stage of CKD. The median and I and III quartiles of KI were 4.0 (1.0-0.8) in all patients, 2.0 (0.0-5.0) in CKD2, 4.0 (0.0-8.5) in CKD3 and 4.5 (2.0-10.0) in CKD4 (p: NS). Twenty five out of 115 pts (22%) had KI= 0; 4/13 (31%) in CKD2, 19/72 (26%) in CKD3 and 2/30 (7%) in CKD4 (CKD3 vs CKD4 p<0.024). KI correlated significantly with age (p <0.001) and was significantly higher in pts with diabetes: 5,0 (1,0-11,0) vs 3.0 (1.0-7.0)(p=0.041) and marginally not significant in those with PVD 7.0 (2.0-10.0) vs 3.0 (0.2-7.0) (p = 0.053). No statistically significant association were found with IHD, smoke, serum Ca, P, PTHi, and 25OH vitD3.
Conclusions: AVC is present since the early stages of chronic kidney disease and shows a significant progression according to CKD stage from CKD2 and CKD3 to CKD4 in spite of not significantly different values in calcium phosphate and PTH.

FP250 HYPERCALCEMIA A RISK FACTOR FOR RENAL TRANSPLANT DYSFUNCTION

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Introduction and Aims: Hypercalcaemia is a complication of chronic kidney disease and there is some evidence that hypercalcaemia can affect renal transplant outcome ? 1,2. We studied our renal transplant cohorts who were followed up in our transplant centre between 1995 - 2005 for at least 3 years.
Methods: Out of 1153 patients who were transplanted within this period, 548 were followed up at our hospital for at least three years post transplant. These patients were identified by our electronic database and were included in our study. We divided theses patients into two groups. Group A (n=426) included patients where calcium was less than 2.5mmol/L at transplant and Group B(n=122) had patients with corrected calcium of more than 2.5mmo/l at the time of transplant.
Results: In Group A, 42 out of 426 patients (9.85 %) were on dialysis within five years after transplantation. In Group B , 14 out of 122 patients (11.47%) were on dialysis within five years . There is also a suggestion from our data (Table 1) that patients who are transplanted with a corrected calcium more than 2.5 mmol/ltr-Group B tend to have a higher creatinine at 1, 2 and 3 years time, but this did not meet statistical significance(P value=0.67)
Conclusions: It is difficult to conclude if high calcium is an independent risk factor due to direct effect of vasconstruction1, or long term secondary to vascular calcification3 or just reflects poorly controlled renal bone disease and generally have had renal disease longer. We feel renal bone disease including hypercalcemia is difficult to manage post transplant and the best way to prevent hypercalcemia affecting graft function is focusing on renal bone disease during the work up towards transplantation.

References:
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2. Özdemir FN et al: Persistent hypercalcemia is a significant risk factor for graft dysfunction in renal transplantation recipients. Transplant Proc 38: 480–482, 2006
3. Gwinner W et al, Early calcification of renal allografts detected by protocol biopsies: Causes and clinical implications. Am J Transplant 5: 1934–1941, 2005

FP250 Table 1 Numerical values are creatinine levels at 0,1,2 and 3 years post transplantation

	Time 0	1 year	2 year	3 year
Group A				
Median	750.05	133.8	136.1	137.45
Mean	769.2311	151.4332	154.2141	156.9962
Group B				
Median	828.4	141.65	143.4	141.95
Mean	819.6843	165.7074	172.8509	158.7565

FP251 AUTONOMOUS HYPERPARARHYROIDISM IN CKD STAGES 3-4 TREATED WITH CINACALCET

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Introduction and Aims: Autonomous (primary) hyperparathyroidism (HP) is being increasingly recognized at earlier stages in the general population. It is necessary to emphasize that in an outpatient nephrology clinic, even not devoted to lithiasis, autonomous HP (primary or more rarely tertiary) should also be considered in patients with CKD. The aim of this study is to analyze the effect of cinacalcet (Ct) on a significant group of patients with coexistent CKD stages 3-4 and autonomous HP.
Methods: Thirty eight patients were referred to our hospital for the presence of CKD stages 3-4 and were also diagnosed of autonomous HP during follow-up, initially treated with cinacalcet (Mimpara®). Patients were unwilling to undergo, ineligible for, or in the waiting list for parathyroidectomy (PTX). Autonomous HP was diagnosed by the presence of hypercalcemia and an inappropriately high or inadequately suppressed intact parathyroid hormone levels (PTH, Roche). Patients with CKD 5, or receiving calcium (Ca), vitamin D derivatives, thiazides, lithium and/or other related treatments were excluded. Eighteen patients were not considered eligible for surgical or medical treatment. Variables were collected before treatment and after the last control while receiving Ct. Results are expressed as mean±SD,(range). A non-parametricWilcoxon signed–rank test was used and a $p < 0.05$ was considered significant.
Results: Twenty patients (73±10 y/o, 80% female, 65% Tc-sestamibi positive, 30% with a past history of lithiasis, 59% vitamin D insufficient and 36% deficient,) were diagnosed of both CKD 3-4 and autonomous HP. Starting dose of Ct varied between 30 mg e.o.d. to 30mg/12 hours. The mean final dose was 37±30 mg/24 hours (15-120mg) after 1.3±1.0 y of follow-up (35-1290d). Ca decreased from 2.78 ± 0.22 mmol/L (2.59-3.49) to 2.55 ± 0.21 (2.24-3.09) ($p < 0.0001$) after Ct. Ca decreased to 2.48 ± 0.10 excluding 3 intolerant patients and 1 non-responder. No differences were observed in PTH (282 ± 220 pg/ml vs 219 ± 177) (NS), phosphate, GFR (basal 38 ± 11 ml/min/1.73 m2), urinary Ca or calcidiol levels before and after Ct treatment. Four patients undergone a successful PTX (54-653d) after starting Ct. Early PTX (54d) was performed in 1 patient with severe hyperCa resistant to 120 mg/day of Ct, and in 1 patient PTX was performed (184d) because of intolerance to Ct. 2 additional elective PTXs were performed. Intolerant patients (15%) had Ct withdrawn because of abdominal pain or diarrhoea. Other moderate and mild adverse events were unfrequent, moderate or mild, and transient. Sustained improvement in mental status and well being was reported in 25% of patients
Conclusions: 1) Autonomous HP should be considered in patients with CKD who exhibit even mild unexpected elevations of serum Ca; 2) Even low doses of Ct are safe and effective in decreasing plasma Ca in patients with CKD and autonomous HP when they are ineligible for, unwilling to undergo, or in the waiting list for PTX. 3) Not uncommon clinical improvement is observed in these patients, even with mild hyperCa, but intolerance or resistance to cinacalcet may potentially limit its use.4) Potencial benefits from avoiding hyperCa on the evolution of CKD or morbimortality in this population are yet to be determined.

FP252 BONE DISEASE IN NEWLY DIAGNOSED LUPUS NEPHRITIS PATIENTS

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Introduction and Aims: Bone disease is an important and preventable condition related to systemic lupus erythematosus (SLE). The role of glucocorticoid therapy as

FP252 Table 1 Clinical and histomorphometric parameters of SLE patients and controls.

	Patients (n=8)	Controls (n=16)	p*
Clinical features			
Age (years)	30,5±10,4	30,4±9,8	0,85
Histomorphometric parameters			
Structure			
BV/TV (%)	26,51±7,87	25,69±5,56	0,95
Tb.Th (µm)	134,39±24,16	122,64±20,45	0,46
Tb.Sp (mm)	390,77±99,79	366,94±101,25	0,54
Tb.N (mm)	1,95±0,32	2,1±0,38	0,35
Formation			
OS/BS (%)	2,13 (0,98-12,61)	8,6 (6,6-16,1)	0,05
Ob.S/BS (%)	0,21 (0,09-0,78)	0,75 (0,07-2,37)	0,34
OV/BV (%)	0,11 (0,04-0,71)	1,57 (1,06-2,92)	**0,004***
O.Th (µm)	2,74±1,17	11,3±2,07	**<0,001***
Resorption			
ES/BS (%)	8,27 (4,71-11,55)	1,9 (1,3-3,1)	**<0,001***
Oc.S/BS (%)	0,3 (0,19-0,71)	0,01 (0-0,1)	**<0,001***

the major event in bone loss has been questioned by recent studies. However, the methodology of most of these studies included only evaluation of bone mineral density by X-ray absorptiometry. The aim of this study was to evaluate bone disease using histomorphometric parameters in newly diagnosed SLE patients.
Methods: We included pre-menopausal female patients with =2 months of diagnosed SLE and Lupus Nephritis (LN) according to the American College of Rheumatology classification criteria. Exclusion criteria were: estimated GFR (MDRD) < 30 ml/min/1,73m2 and previous use of drugs that affect bone metabolism (as calcium supplements, anticonvulsants and anticoagulants). Patients were submitted to bone biopsy and histomorphometry analysis was performed according to the American Society for Bone and Mineral Research. The 8 patients included from 2011 January to December were compared to 16 gender and age-matched controls from a Brazilian bone database of healthy individuals (Dos Reis et al. Bone 1998; 23: S476).
Results: Patients presented a mean age of 30.5±9.7 years, with a BMI of 23.1±3.0 Kg/m2. They were on glucocorticoid treatment for 35.3±11.5 days, with a cumulative prednisone dose of 5614.4±2039.8 mg. Seven patients (87.5%) presented focal or diffuse proliferative LN and one patient presented membranous LN. Mean 24h proteinuria was 6.0±.1.9 g, with a serum albumin of 2.0±0.7 g/dL and an estimated GFR of 65.1±34.5 ml/min/1.73m2. All patients presented vitamin D deficiency (serum 25-hydroxyvitamin D = 8.8±2.7 ng/ml, range 4-12), probably contributing to an increased iPTH levels (79.4±59.5 pg/ml). Histomorphometric parameters of patients and controls are shown in table 1. We observed that SLE patients presented lower OV/BV and O.Th, suggesting a reduced bone formation. These patients also presented higher ES/BS and Oc.S/BS, revealing an increased bone resorption.
Results are expressed as: mean±std or median (25-75 IQR). BV/TV= trabecular volume; Tb.Th= trabecular thickness; Tb.Sp= trabecular separation; Tb.N= trabecular number; OS/BS= osteoid surface; Ob.S/BS= osteoblast surface; OV/BV= osteoid volume; O.Th= osteoid thickness; ES/BS= eroded surface; Oc.S/BS= osteoclast surface.
Conclusions: Newly diagnosed LN patients presented a reduced bone formation associated with an increase in resorption parameters. We believe these findings could not be attributed to glucocorticoid use and might actually be related to the active inflammation involved in LN physiopathology.

FP253 PRO-INFLAMMATORY CYTOKINES AND BONE FRACTURES IN CKD PATIENTS. A PROSPECTIVE SINGLE CENTRE STUDY

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Introduction and Aims: Pro-inflammatory cytokines are thought to play significant roles in regulating bone remodeling and the risk of bone fractures is increased in several diseases characterized by chronic inflammation. Inflammation has been consistently found to be common in CKD- 5D patients, but the relationship between pro-inflammatory cytokines and fractures in CKD- 5D patients is undefined. We studied the relationship between incident bone fractures and inflammatory cytokines in a cohort of CKD-5D patients.
Methods: In 100 CKD-5D patients (66 on HD, 34 on CAPD; males:63, females:37; mean age: 61+15; median dialysis vintage: 43 months) belonging to a single renal Unit, we determined at enrolment bone metabolic parameters (intact and whole PTH, bone and total alkaline phosphatase, calcium, phosphate) and inflammatory cytokines (TNFalfa, IL-6, CRP). Patients were followed-up until the first symptomatic fracture. None of patients studied had undergone parathyroidectomy. At time of enrolment patients had to be in stable conditions and free of acute inter-current diseases.
Results: CRP levels were above the upper normal limit in as much as 67% of the patients. During follow-up 18 patients experienced a first symptomatic fracture. On categorical analysis these patients had significantly (p=0.04) higher intact PTH levels (median: 319 pg/ml IQ range: 95- 741) compared to patients without fractures (135 pg/ml IQ: 53-346). Similarly patients with fractures had higher TNF alfa levels (median: 12 pg/ml IQ: 6.4-13.4 vs 7.8 pg/ml IQ: 4.6-11; p=0.02). On bivariate Cox analysis both TNF alfa and intact PTH were independent predictors of symptomatic bone fractures. TNF alfa association with incident fractures, on bivariate analyses, was also independent of previous fractures, age, sex, previous kidney transplants, and serum albumin.
Conclusions: These preliminary analyses would support the hypothesis that pro-inflammatory cytokines play a role in the increased risk of bone fractures in CKD-5D patients. Analyses in larger cohorts and with adequate number of events are needed to firmly establish the TNF-fracture link emerged in the present study.

FP254 STRIKING AND PROMISING MIS-SENSE MUTATIONS ON THE GNAS1 GENE EXONS' 1,4,10 AND 4 IN SAGLIKER SYNDROME (SS). A UNIQUE CATASTROPHIC ENTITY . CYTOGENETIC STUDIES FOR CHROMOSOMAL ABNORMALITIES ,CASR GENES AND GNAS 1 MUTATIONS. INTERNATIONAL EVALUATION OF UNRECOGNIZABLY UGLYFYING HUMAN FACES IN LATE AND SEVERE SH IN CKD.

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Introduction and Aims: Sagliker syndrome is new syndrome composed by CKD, SH,unrecognizably uglifying human face appearances ,shortness, irregularly scattered skull and face bones deformities, destruction of nasal and maxillary bones,irregularly located teeth in mouths, soft and innocent tissue accumulations in upper oral cavities,upward curved finger tips,grade two maloclusion of maxillary bones (frontal forward malformation of upper jaws),x-knee type deformations and walkings, deformities on scapulas,neurologic and psyciatric problems,hearing abnormalities and was described first in 2004 (Fig.1).
Methods: Essentially this is an international study with 60 patients from different partsof globe such as Turkey, India, Maleysia, China, Romania, Egypyt, Tunisia, Taiwan,Mexico, Algeria, Poland, Russia and Iran.We took samples from patients and first degree relatives and PTH,Ca,Po4,ALP, Vit D, calcitonin, all x-rays including cephalometric and bone densitometric studies, hemoglobin electrophoresis,G6PD levels,T3 , T4, TSH, growth hormon, FSH, LH,total testosteron levels were evaluated.

FP254 Figure 1. Some and partly covered pictures of unrecognizably uglyfying human faces in late and severe SH in CKD. Sagliker syndrome (SS) . A Unique Catastrophic Entity .

FP254 Table 1 The GNAS1 Mutations of Patients with Sagliker Syndrome

Patient	Exon	Codon	Nucleotide sequence	Amino acid change	
1	1	284	AGC	ACC (Ser→Thr)	Missense mutation
1	10	878	GCC	GCA	Nonsense mutation
6	4	765	CCC	CCA	Nonsense mutation
12	4	750	ATT	ACT (Ile→Thr)	Missense mutation
20	10	885	ATG	ATA (Met→Ile)	Missense mutation
22	10	854	GGT	GGC	Nonsense mutation
23	4	769	TTC	TGC (Phe→Cys)	Missense mutation

Major chromosom abnormalities by cytogenetic analyses , CaSR genes and GNAS 1 gene mutations' studies by particularly focusing on exons 1,4,5, 7,10,13 were performed . Some of exons might be responsible for hereditary bone distrophies-achondroplasias although our patients were not resembling to any but they could be in between.

Results: We did not find vit D deficiency and low calcitonin levels thought to be responsible. We did not find abnormalities in hemoglobin electrophoresis and G6PD levels.We didn't find thyroid function defects . We didn't find differences in growth hormone levels .We did not find sex hormone differences in FSH, LH and total testosteron levels.We couldn' t find major chromosal abnormalities in patients and relatives in cytogenetical studies and CaSR genes.But we did find GNAS 1 gene mutations in patients with ratio of 40 % .In codon number of 284 of exon 1, amino acid serin was replacing threonin by changing amino acid sequence from AGC to ACC, in codon number of 750 of exon 4, aminoasid ilein was replacing threonin by changing amino acid sequence from ATT to ACT, , in codon number of 885 of exon10, aminoasid methionin was replacing isoleucin by changing amino acid sequence from ATG to ATA and in codon number of 769 of exon4, aminoacid phenilalanin was replacing cystein by changing amino acid sequence from TTC to TGC

Conclusions: New entity called SS is a miserable state with the frequency around % 0,5 in mentionned poor and miserable patients.We din't find any preliminary chromosomal abnormality and any abnormalities on CaSR Genes' Exons 2 and 3, but GNAS 1 gene mutations. Those missense mutations might be extremly important in pathogenesis of SS (Table 1). We thought the cause of osteoporosis and bone diseases in patients was severe, late SH and untimingly late treatment modalities particularly due to monetary deficiencies, sosyo echonomic insufficiencies and moreover unwanted –innocent infortunate iatrogenical mistreatments.Treatments must start as early and proper as possible by squiled personel in sophisticated medical centers with most advanced technologically designed medical novel tools. This is a sine qua non humanity task.