MINERAL METABOLISM ABNORMALITIES AND OUTCOMES IN NON-DIALYSIS CHRONIC KIDNEY DISEASE PATIENTS

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BACKGROUND AND AIMS

Since mineral metabolism abnormalities were related to poor survival in dialysis patients[1], but their impact on clinical outcomes in non-dialysis chronic kidney disease (CKD) was less studied[2], we aimed to assess the long-term influence of biochemical abnormalities (calcidiol, calcium, phosphate, intact parathyroid hormone, total alkaline phosphatase) and vascular calcification/stiffness (ankle-brachial index, cardio-ankle vascular index - CAVI, lumbar aortic calcification score - ACS), as components of CKD-related mineral and bone disorder (CKD-MBD), on both kidney and patient's outcomes, in non-dialysis CKD patients.

METHODS

STUDY DESIGN: Single centre, cohort, retrospective, follow-up 48 (30;53) Mo.

PRIMARY OUTCOMES:

- Time to renal replacement therapy (RRT) initiation;
- Time to occurrence of a composite CV end-point (death or non-fatal stroke, myocardial infarction, or hospitalization for decompensated heart failure).

STATISTICAL ANALYSIS: Kaplan-Meier analysis + baseline Cox regression models (adjusted for age, gender, smoking, medical history, kidney function, proteinuria, malnutrition-inflammation, medications) were performed to evaluate the predictors of survival. $p<0.05$ was considered significant.

SUBJECTS

One hundred thirty-five non-dialysis CKD subjects were selected from those enrolled in a previous multicentric cross-sectional trial. Exclusion criteria were: kidney graft, nephrotic syndrome, systemic immune-inflammatory diseases (lupus erythematosus, vasculitis etc) or immunosuppressive therapy.

Patients' outcome was assessed, by both methods:

- Active (phone contact + medical visit);
- Passive (data retrieved from the Romanian Renal Registry database).

Two subjects were lost of follow-up, so the statistical analysis was carried out on the remaining 133 patients, who were Caucasian adults:

- 60% males, median age 61 (50;71) years, 61% <65 years old;
- median eGFR 33(21;53)mL/min [69% stages 3 and 4 CKD, 61% high and very high risk according to KDIGO classification, 40% vascular nephropathies];
- 74% arterial hypertension, 23% diabetes mellitus, 13% active smoking;
- 72% arterial stiffness (CAVI >9);
- 51% without clinical manifest atherosclerosis,
- 17% advanced arterial calcifications (ACS >5);
- 57% vitamin D deficiency (calcidiol <15ng/mL), 56% high serum parathyroid hormone (>75pg/mL);
- C-reactive protein 3 (2;7)mg/L, serum albumin 4.5 ± 0.4g/dL

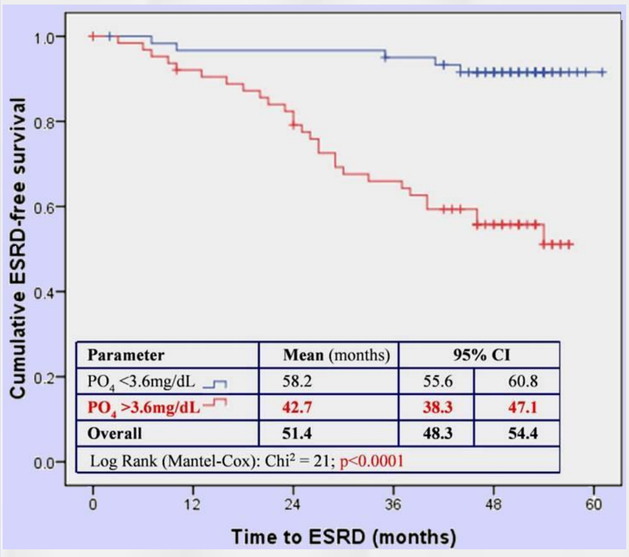
RESULTS

MINERAL METABOLISM ABNORMALITIES AND KIDNEY OUTCOME

24.8% of subjects had started RRT (rate of incidence 7.4/100 patients years)

Subjects who started RRT were younger, more commonly treated with calcium salts, had lower serum albumin and eGFR, but higher proteinuria, C-reactive protein, serum phosphate, alkaline phosphatase, iPTH, left ventricular hypertrophy, and ankle-brachial index.

Higher than median serum phosphate, even in the normal range (3.6 mg/dL), was associated with a reduced RRT-free survival:



Parameter \ CKD-Group	RRT(+) (n=33)	RRT(–) (n=100)	*p*	CV (+) (n=19)	CV (–) (n=114)	*p*
Age (years)	**52(37;64)**	**62(56;73)**	**0.001**	70(60;79)	60(46;70)	0.002
Males (%)	58	61	0.72	26	42	0.19
Diabetes mellitus (%)	24	23	0.88	42	20	0.04
Arterial Hypertension (%)	79	73	0.51	89	73	0.10
Clinical (+) atherosclerosis (%)	48	49	0.67	74	46	0.02
Calcium salts use (%)	**55**	**15**	**<0.001**	37	23	0.19
Vitamin D derivatives use (%)	58	40	0.08	47	44	0.78
eGFR (mL/min)	**15(13;21)**	**39(30;59)**	**0.001**	31(16;42)	34(21;56)	0.17
Urinary albumin-to-creatinine (mg/g)	**1366 (465;2766)**	**36 (10;283)**	**0.001**	585 (19;1389)	60 (14;643)	0.05
KDIGO - Low (%)	39	38	**<0.001**	16	32	0.36
risk - Moderate (%)	3	12		19	9	
categories - High (%)	12	36		26	30	
- Very high (%)	**82**	**14**		39	29	
Serum albumin (g/dL)	**4.2±0.4**	**4.5±0.4**	**0.001**	4.2±0.44	4.5±0.38	0.01
Serum C-reactive protein (mg/L)	**4(3;9)**	**3(2;7)**	**0.04**	3(2;7)	3(2;6)	0.84
Serum phosphate (mg/L)	**4.4(3.7;5.0)**	**3.4(3;3.8)**	**0.001**	4.2(3.3;4.6)	3.5(3;3.9)	0.01
Ionized serum calcium (mg/dL)	4(3.8;4.3)	4(3.9;4.2)	0.74	4.2(3.8;4.4)	4(3.9;4.2)	0.32
Serum intact PTH (pg/mL)	**264(111;416)**	**74(50;119)**	**0.001**	84(47;294)	85(51;187)	0.76
Serum calcidiol (ng/mL)	13(9;16)	14(10;20)	0.41	12.8(7;19)	13.9(10;20)	0.11
Serum alkaline phosphatase (UI/L)	**99(75;120)**	**70(61;98)**	**0.003**	99(68;117)	77(61;103)	0.07
Cardio-ankle vascular index	10.1(9;11.6)	10.2(9;12)	0.85	9.3(8.1;11)	10.3(9;12)	0.23
Ankle-brachial index	**1.1(1;1.17)**	**1.05(1;1.1)**	**0.04**	1.1(1;1.17)	1.1(1;1.13)	0.41
Lumbar aortic calcification score	0(0;5)	0.5(0;3.5)	0.68	1(0;4)	0(0;4)	0.85
Interventricular septum (mm)	**12(9;13)**	**10(9;12)**	**0.03**	12(10;13)	10(9;12)	0.05

After adjusting for all covariates, the independent predictors of RRT initiation were higher serum phosphate, arterial stiffness (as suggested by higher ankle-brachial index), higher left ventricular hypertrophy and younger age.

Although kept in the final model, neither the KDIGO risk categories nor iPTH did reach the statistical significance ($p=0.08$ and $p=0.09$, respectively):

Variable	*B*	*SE*	*Exp(B)*	*95% CI for Exp(B)*	*p*
Log (Age)	–1.57	0.62	0.21	0.06 to 0.70	0.01
Log (PO4)	3.52	0.91	33.73	5.63 to 201.9	<0.001
Log (IVS)	1.93	0.82	6.89	1.39 to 34.24	0.02
Log (ABI)	9.37	4.39	1.2E+04	2.18 to 6.4E+07	0.03
$Chi^2 = 81$, $p<0.001$					

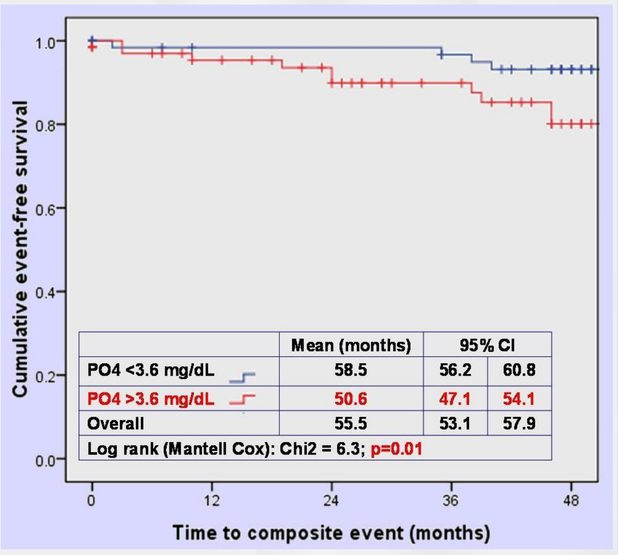
PO4: serum phosphate; IVS: Interventricular septum; ABI: Ankle-brachial index.

MINERAL METABOLISM ABNORMALITIES AND PATIENT'S OUTCOME

14% of subjects reached CV end-point (rate of incidence 4.5/100 patients years)

The composite outcome, opposite to the kidney outcome, was reached by older subjects, with higher prevalence of diabetes mellitus and clinical manifest atherosclerosis, higher proteinuria, serum phosphate and left ventricular hypertrophy, but lower serum albumin, irrespective of eGFR.

Higher than median serum phosphate, even in the normal range (3.6 mg/dL), was associated with a lower CV event-free survival:



Cox analysis showed that older age, lower serum albumin and higher serum phosphate independently predicted the composite CV outcome. Thus, serum phosphate appears as a significant marker of cardiovascular morbidity and all-cause mortality in non-dialysis CKD patients, along with well accepted influence of age (one of the traditional risk factors) and of the parameters of malnutrition-inflammation (e.g. lower serum albumin):

Variable	*B*	*SE*	*Exp(B)*	*95% CI for Exp(B)*	*p*
Log (Age)	2.29	1.16	9.87	1.01 to 96.70	0.05
Log (PO4)	1.77	0.86	5.89	1.09 to 31.74	0.04
Serum albumin	–1.46	0.71	0.23	0.06 to 0.94	0.04
$Chi^2 = 22$, $p<0.001$					

PO4: serum phosphate.

CONCLUSIONS

Serum phosphate was the only mineral metabolism abnormality associated with an increased risk for both adverse kidney and overall outcome in non-dialysis CKD subjects with a high prevalence of arterial hypertension and arterial stiffness, but without significant inflammation and with relatively low diabetes mellitus and atherosclerosis burden. Accordingly, phosphatemia remains a prioritary therapeutic target.

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