PHOSPHATE LOAD PER FUNCTIONING RENAL UNIT PREDICTS ACCELERATED RENAL FUNCTION LOSS INDEPENDENTLY OF FGF-23 AND OTHER RISK FACTORS IN STAGE 2-5 CKD PATIENTS

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OBJECTIVES

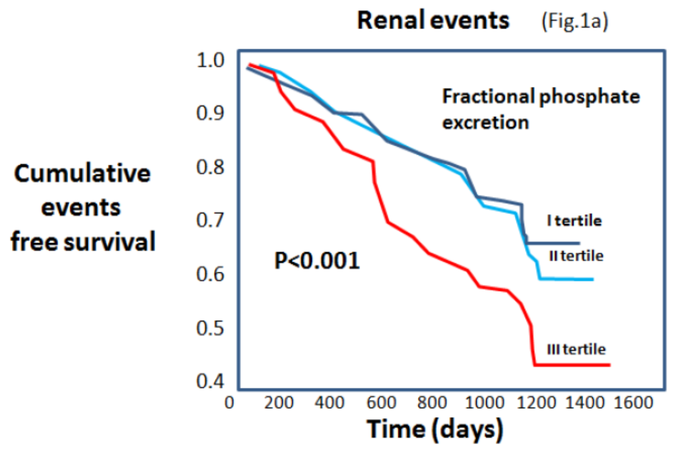
Hyperphosphatemia is a predictor of accelerated renal function loss in patients with chronic kidney disease (CKD). This phenomenon could be interpreted as the trade-off of a counter-regulatory response aimed at maintaining global phosphate balance. The background hypothesis is that global phosphate balance is maintained by raising phosphate excretion per functioning renal unit (fractional phosphate excretion) and is possibly mediated by high FGF23. However, this hypothesis has never been formally tested in appropriate cohort studies.

METHODS

We studied 494 incident patients with stages 2-5 CKD (age 62 11 years, 60% males and 32% diabetics).
The baseline eGFR in this cohort was 28.4 13.9 ml/min/1.73m^2.
The study end-point was a composite renal outcome (i.e. eGFR reduction > 30%, dialysis or transplantation).

FIGURES

Renal events (Fig.1a)



Cox regression analysis (Model based on Fractional phosphate excretion as continuous variable) (Fig.1b)

Variables	Units of increase	Crude Hazard ratio and 95% CI, P value	Adjusted Hazard ratio and 95% CI, P value
Fractional phosphate excretion	5%	1.06 (1.03-1.09), P<0.001	1.05(1.02-1.07), P<0.001
Age	1 year		1.00(0.98-1.02), P=0.94
Gender	0=F; 1=M		0.81(0.54-1.23), P=0.33
Smoking	0=no; 1=yes		1.20(0.81-1.77), P=0.36
Diabetes	0=no; 1=yes		0.78(0.53-1.17), P=0.23
Serum Cholesterol	10 mg/dL		0.96(0.93-0.99), P=0.02
Systolic BP	1 mmHg		1.01(0.99-1.02), P=0.06
Urinary protein	1 g/24h		1.51(1.37-1.67), P<0.001
Serum Phosphate	1 mg/dL		1.58(1.29-1.93), P<0.001
Anti-hypertensive treatment	0=no; 1=yes		0.62(0.23-1.73), P=0.36

RESULTS

Fractional phosphate excretion (median: 41%, interquartile range 27-61%) was above the upper limit of the normal range (>20%) in the majority of CKD patients (83%). In unadjusted analyses, fractional phosphate excretion was related directly to urinary protein (rho=0.24, P<0.001), FGF-23 (r=0.25, P<0.001), male gender (r=0.13, P=0.003), smoking (r=0.13, P=0.004) and diastolic blood pressure (r=0.09, P=0.04) and inversely to eGFR (r=-0.44, P<0.001) and diabetes (r= -0.11, P=0.02). Fractional phosphate excretion was largely unrelated to serum phosphate (r=-0.03, P=0.54).
During the follow-up (mean: 2.4 years), 165 renal events occurred. In a Kaplan-Meier survival analysis, the incidence rate of renal events increased from the first tertile of fractional phosphate onwards (Fig.1a). Furthermore, in a crude analyses, an increase in fractional phosphate excretion as continuous variable (5%) was associated to a 6% increase in the hazard ratio (HR) of renal events (HR: 1.06, 95%: 1.03-1.09, P<0.001). Data adjustment for potential confounders (age, gender, smoking, diabetes, cholesterol, diastolic pressure, urinary protein, phosphate, anti-hypertensive treatment and FGF23) did not affect the strength of the relationship between fractional phosphate excretion and renal outcomes (HR: 1.05, 95% C: 1.02-1.07, P<0.001) (Fig.1b)

CONCLUSIONS

Fractional phosphate excretion is a strong, independent predictor of incident renal events. The predictive power of this parameter is largely independent of other risk factors, including serum phosphate and FGF23. Phosphate burden per functioning renal unit, predicts progression towards end-stage kidney disease through yet unknown mechanism(s). Biological pathways independent of FGF-23 most likely play a dominant role in phosphate-related renal damage.

51ERA-EDTA
172--MP
H) Clinical Nephrology, CKD. H2) General and Clinical Epidemiology and CKD 1-5.
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DOI: 10.3252/pso.eu.51era.2014
Poster presented at: 51 ERA-EDTA CONGRESS AMSTERDAM 2014