Severe dietary phosphorus restriction is associated with reduced FGF23 levels in uremic rats

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INTRODUCTION

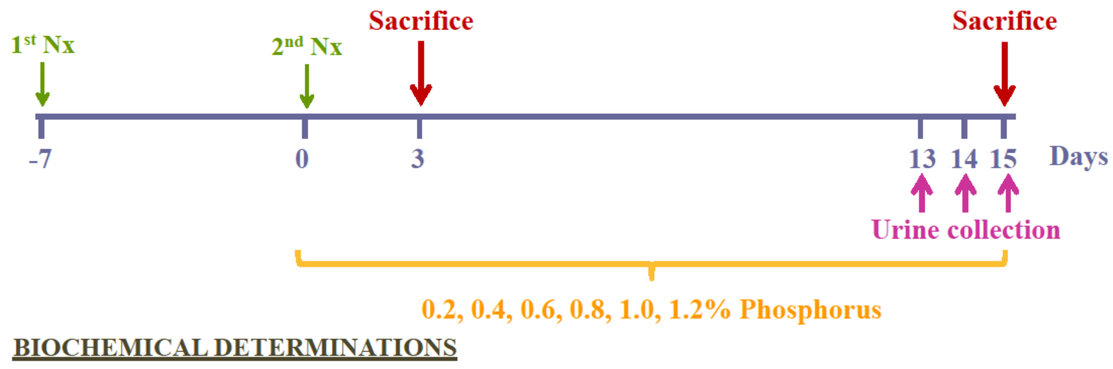
Fibroblast Growth Factor 23 (FGF23) is a potent regulator of phosphorus and vitamin D metabolism. FGF23 increases from early stages of chronic kidney disease (CKD), as a mechanism to counteract phosphorus retention[1].

A reduction in FGF23 levels have been achieved by dietary phosphorus control in healthy volunteers[2], but not always[3]. The administration of phosphorus binders in CKD patients has also been shown to reduce FGF23[4,5] .

We <u>hypothesized</u> that strict control of dietary P should prevent the increase in FGF23 associated to uremia.

The <u>objective</u> of the present study was to determine, in an experimental model of uremia based on 5/6 nephrectomy, to what extent FGF23 production is modified by the intake of dietary phosphorus.

METHODS



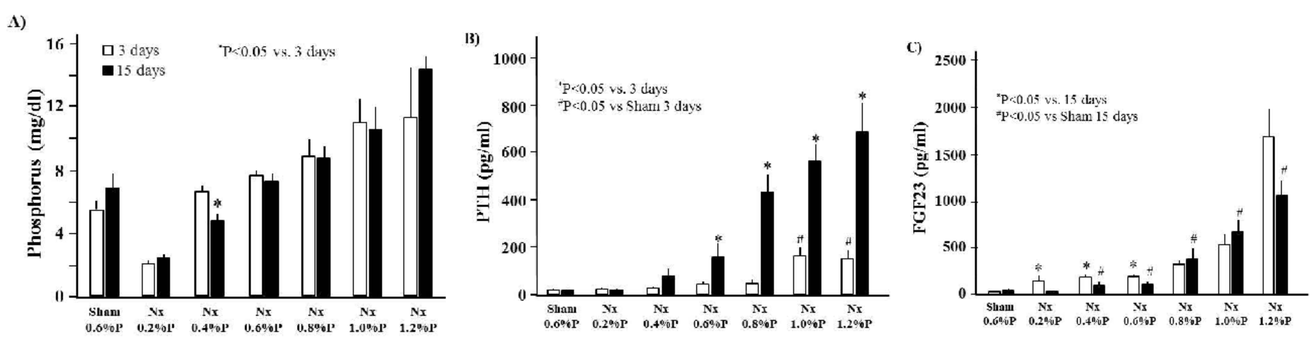
<u>BIOCHEMICAL DETERMINATIONS</u>

- Plasma ionized calcium (selective electrode).
- Plasma phosphorus and creatinine (spectrophotometry).
- Urine calcium, phosphorus, and creatinine (spectrophotometry).
- Plasma FGF23 and PTH (ELISA).
- $1,25(OH)_2D_3$ (HPLC).

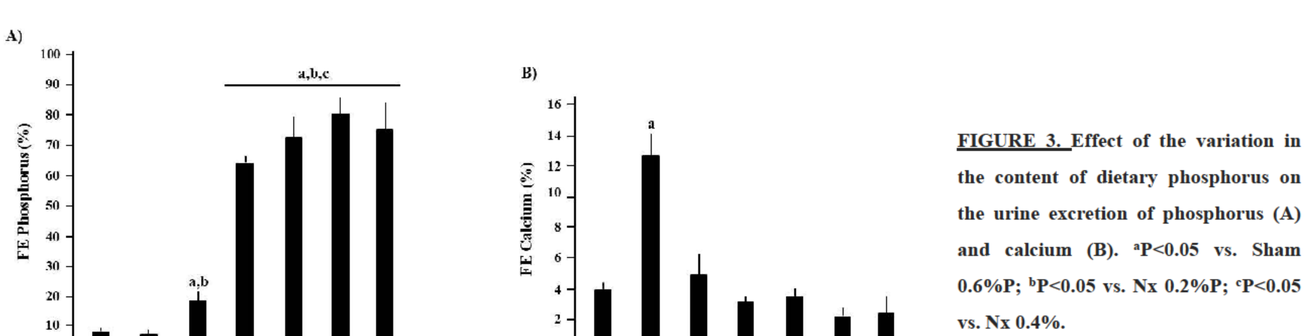
RESULTS

		Sham 0.6%P	Nx 0.2%P	Nx 0.4%P	Nx 0.6%P	Nx 0.8%P	Nx 1.0%P	Nx 1.2%P
Cr (mg/dl)	3 days	0.40±0.02	1.50±0.10[a,b,*]	1.36±0.10[a,b,*]	1.82±0.23[a,b,*]	1.40±0.19[a,b,*]	1.12±0.11[a]	2.44±0.75[a]
	15 days	0.34±0.05	1.05±0.10[a]	0.93±0.16[a]	0.89±0.08[a]	0.93±0.06[a]	1.07±0.11[a]	1.18±0.17[a]
Ca^{2+} (mM)	3 days	1.32±0.04	1.21±0.03	1.25±0.01	1.20±0.02	1.26±0.02	1.03±0.03[a,*]	0.92±0.03[a,b]
	15 days	1.28±0.02	1.30±0.02	1.23±0.03	1.22±0.01	1.26±0.03	1.12±0.03	0.87±0.06[a,b]
$1,25(OH)_2D_3$ (pg/ml)	3 days	168±25	113±18	208±48	232±31	193±44[*]	128±45[*]	58±7[a,b,*]
	15 days	188±50	189±17	193±26	294±50	279±23	66±26[a]	78±22[a,b]

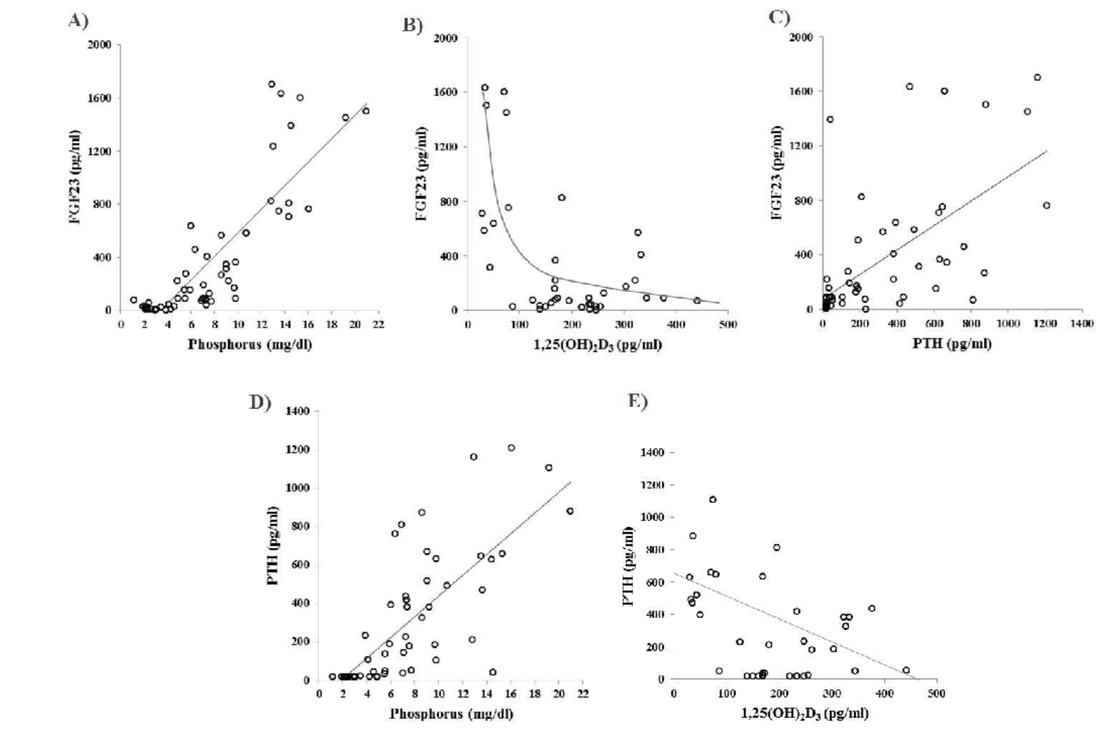
<u>TABLE 1.</u> Serum levels of creatinine, ionized calcium and $1,25(OH)_2D_3$ in experimental groups of sham and nephrectomized rats on different diets (N=8-12 animals per group). Data are expressed as mean±SEM. [a]P<0.05 vs. Sham 0.6%P; [b]P<0.05 vs Nx 1.0%P; [*]P<0.05 vs same diet at 15 days.



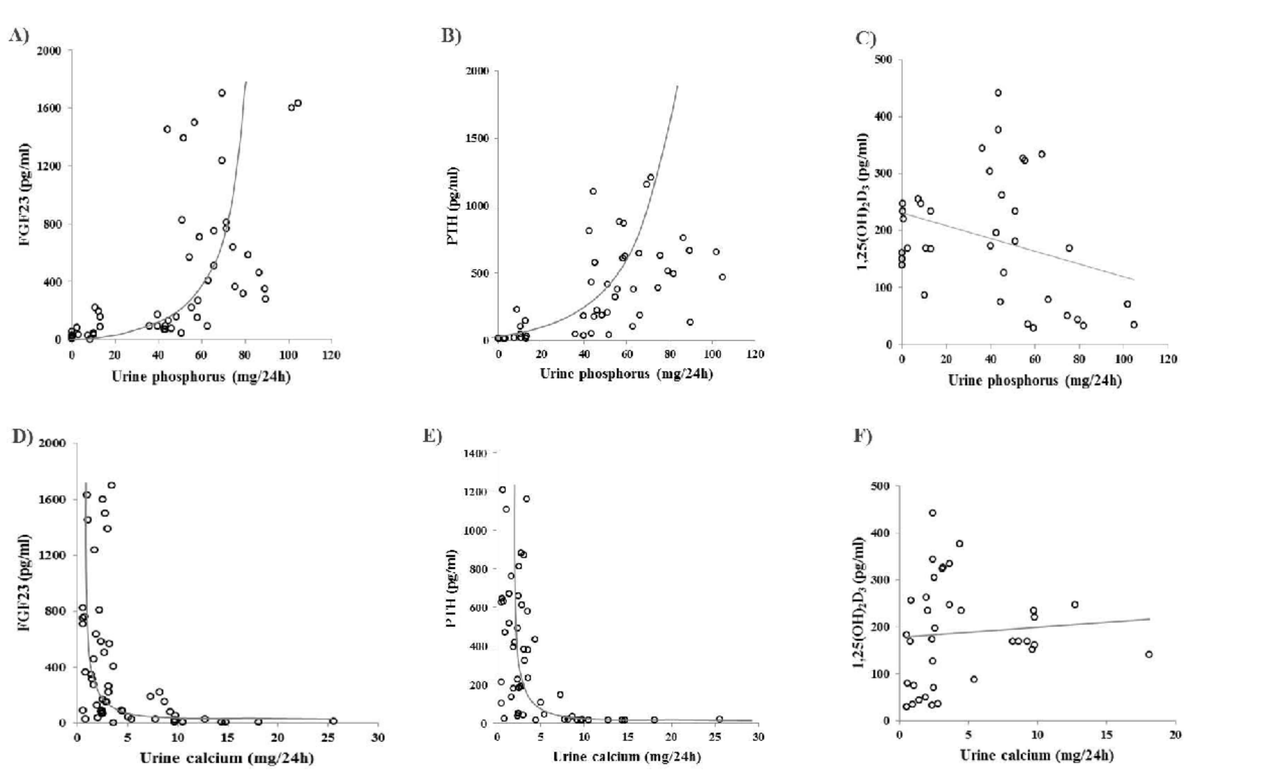
<u>FIGURE 1.</u> Serum levels of phosphorus, PTH, and FGF23 in sham operated rats on a diet with normal phosphorus content (0.6%) and nephrectomized rats receiving diets with phosphorus ranging from 0.2% to 1.2% for either 3 or 15 days. A) [*]P<0.05 vs. 3 days. B) [*]P<0.05 vs. 3 days; [#]P<0.05 vs. Sham 0.6%P 3 days. C) [*]P<0.05 vs. 15 days; [#]P<0.05 vs. Sham 0.6% 15 days.



<u>FIGURE 3.</u> Effect of the variation in the content of dietary phosphorus on the urine excretion of phosphorus (A) and calcium (B). [a]P<0.05 vs. Sham 0.6%P; [b]P<0.05 vs. Nx 0.2%P; [c]P<0.05 vs. Nx 0.4%.



<u>FIGURE 2</u>. Correlation analysis of FGF23 and PTH with other analytes. FGF23 significantly correlated with A) plasma phosphorus (P<0.001; r^2=0.671), B) $1,25(OH)_2D_3$ (P<0.001; r^2=0.198), and C) PTH (P<0.001; r^2=0.237). PTH was directly associated with D) plasma phosphorus (P<0.0001; r^2=0.458) and E) inversely with $1,25(OH)_2D_3$ (P<0.001; r^2=0.268).



<u>FIGURE 4.</u> Correlation analysis between urine phosphorus and calcium and plasma levels of FGF23, PTH, and $1,25(OH)_2D_3$ at 15 days. Phosphorus excretion, expressed as mg/24h was significantly associated with FGF23 (A) (P<0.001, r^2=0.628) and PTH (B) (P<0.001, r^2=0.686), but not with $1,25(OH)_2D_3$ (C) (P=0.068, r^2=0.098). Similarly, a significant association was found between calcium excretion and FGF23 (D) (P<0.002, r^2=0.408) and PTH (E) (P<0.001, r^2=0.481) but not with $1,25(OH)_2D_3$ (F) (P=0.644; r^2=0.006).

CONCLUSIONS

1. **Severe phosphorus restriction prevents the rise in FGF23 production associated to uremia.**
2. **In this experimental model, the elevation in FGF23 occurs before the increase in PTH levels.**

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