Long term phosphate loading and endothelial function:
a single blind, cross-over trial

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1. Background

Phosphate is a cardiovascular risk factor in CKD and in the healthy population. This may relate to a deleterious effect of phosphate on endothelial function. Acute phosphate loading with a high phosphate meal impairs endothelial function but the effect of sustained short term phosphate loading on endothelial function has never been studied. We studied the effect of sustained phosphate loading and phosphate binding medication and endothelial function in healthy volunteers in a cross-over trial.

2. Methods

Healthy volunteers attended for a baseline and 2 subsequent visits. Prior to each visit a 24 hour urine collection was performed for urinary electrolytes and cGMP. Bloods were drawn for routine biochemistry, vitamin D, PTH and FGF-23. Pulse wave velocity, analysis and flow mediated dilatation (FMD) were recorded at each visit. Volunteers were randomised at visit 1 to receive phosphate sandoz (PS) or lanthanum carbonate (LC) for two weeks prior to visit 2. After a wash out period, volunteers then took the other drug before attending for a final visit. (Figure 1)

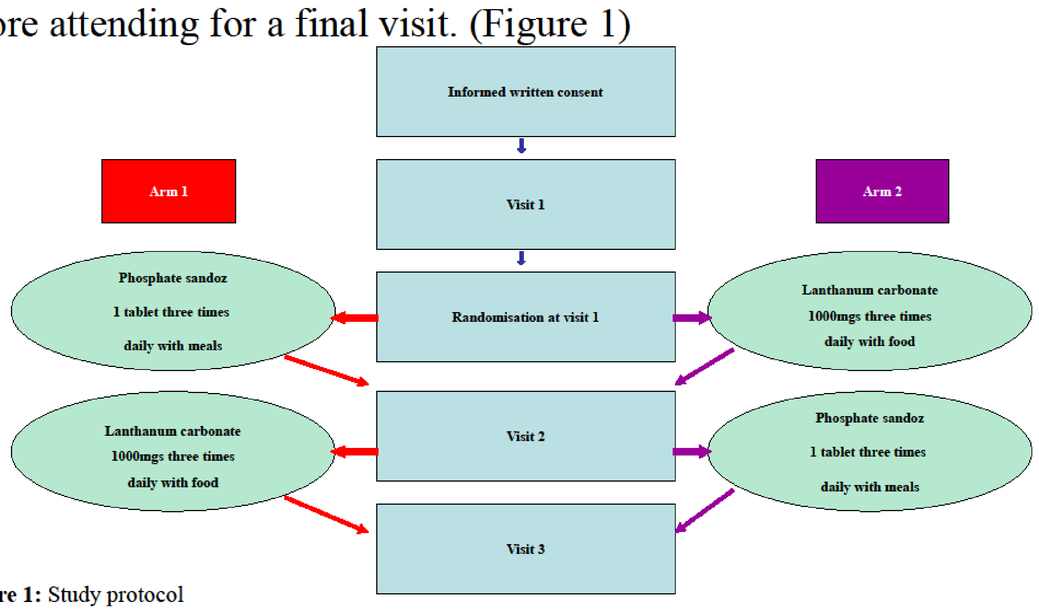

Figure 1: Study protocol

3. Results

There were 19 participants, of whom 63% (n=12) were female. Patient demographics at baseline and following each drug are illustrated in Table 1. After PS, there was a trend towards a higher serum phosphate within the normal range. FGF-23 and FeP rose significantly compared to baseline (p=0.013, p<0.001). Urinary cGMP correlated negatively with serum phosphate (p=0.003). As shown in figure 2, FMD post cuff inflation reduced significantly (3.38% (IQR 2.57-5.26%), p<0.001).

Parameter	Baseline	Post lanthanum	Post phosphate sandoz	p value
Age (years)	42.2 ±14.3			ns
Males	36.8% (n=7)			ns
BMI	26.02 ± 4.12	26.3 ± 3.86	26.3 ± 3.84	ns
Systolic blood pressure (mmHg)	123.1 ± 15.8	122.9 ± 10.3	119.81 ± 16.8	ns
Diastolic blood pressure (mmHg)	74.5 ± 10.5	75.2 ± 9.4	74.1 ± 12.1	ns
Creatinine (mmol/L)	66.4 ± 6.3	65.8 ± 6.8	65.8 ± 6.6	ns
Adj. Calcium (mmol/L)	2.35 ± 0.07	2.36 ± 0.05	2.34 ± 0.09	ns
Phosphate (mmol/L)	1.05 ± 0.18	1.03 ± 0.18	1.06 ± 0.16	ns
Vitamin D3 (nmol/L)	48.2 ± 23.3	40.3 ± 20.6	45.6 ± 25.8	ns
PTH	5.9 ± 2.1	5.78 ± 1.36	6.4 ± 2.3	ns
FGF-23 (RU)	***49.7 (45.9-69.1)***	***59.1 (38.2-73.4)***	***66.6 (50.0-84.9)***	*0.028*
%change from baseline FGF-23		***-1 (-19.8-21.7)***	***19.6 (3.1-38.9)***	*0.004*
Fractional excretion of phosphate	***14.3 ± 3.4***	***11.4 ± 4.3***	***28.4 ± 9.2***	*<0.001*
Urinary cGMP(nmol)	472.8 (312 -645.4)	530.6 (288.2-756.4)	501.1 (274.9-674)	ns
Urinary FGF-23 (RU)	46.1 (26.6-288.2)	139.5 (31.3-360.6)	227.9 (39.4-405.8)	ns
FMD post cuff	***8.4 (6.2-11.6)***	***6.6 (3.4-10.3)***	***3.38(2.57-5.26)***	*<0.001*
% change from baseline		***-23.5(-59--0.2)***	***-58.1 (-71.9-43.36)***	*<0.001*
PWV (m/s)	7.4 ± 1.9	7.3 ± 1.7	7.1 ± 1.6	ns

Table 1: Patient demographics at baseline and following intervention

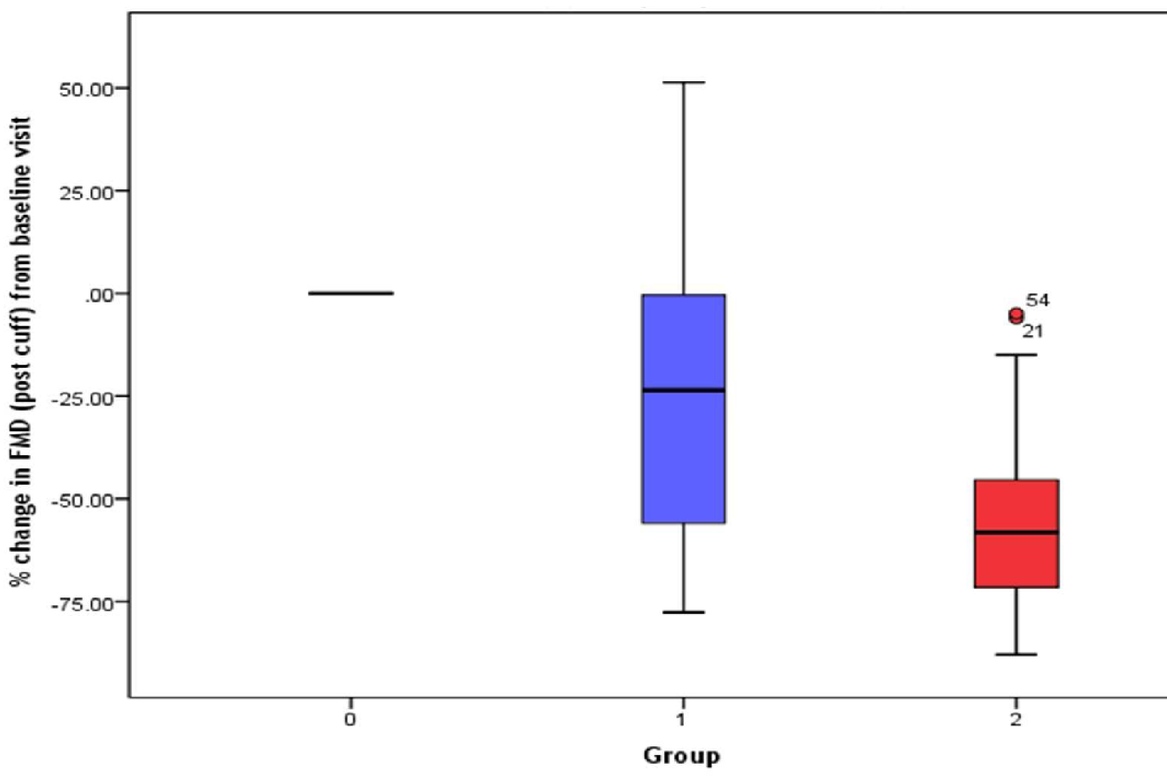

Figure 2: Post cuff FMD as a % change from baseline with each intervention. 0 is th baseline measure, 1 following lanthanum and 2 following phosphate sandoz

Randomisation order had no effect. In a regression model, higher FGF23 were independent predictors of attenuated post cuff inflation FMD as sh 2. Figure 3 illustrates the relationship between FGF-23, FeP and post cuf FMD.

Variable	B	Confidence Interval		p value
		Lower Bound	Upper Bound	
Fractional excretion of phosphate	-1.1	-1.9	-0.2	0.014
Serum FGF-23	-0.5	-0.7	-0.2	0.002

Table 2: Regression model. A multiple regression model was created, the inclusion of serum FGF-23 and urinary fractional phosphate statistically significantly predicted a change in FMD compared with the baseline visit, F (2, 54) = 10.07 p<0.00 Together both variables add statistically significantly to predict the change in FMD (p <0.05).Several models were tried to following variables: systolic blood pressure, serum phosphate, age, sex, urinary FGF-23, urinary calcium and urinary cGM of these factors were significant predictors of the change in post cuff FMD after an intervention compared with the measur baseline.

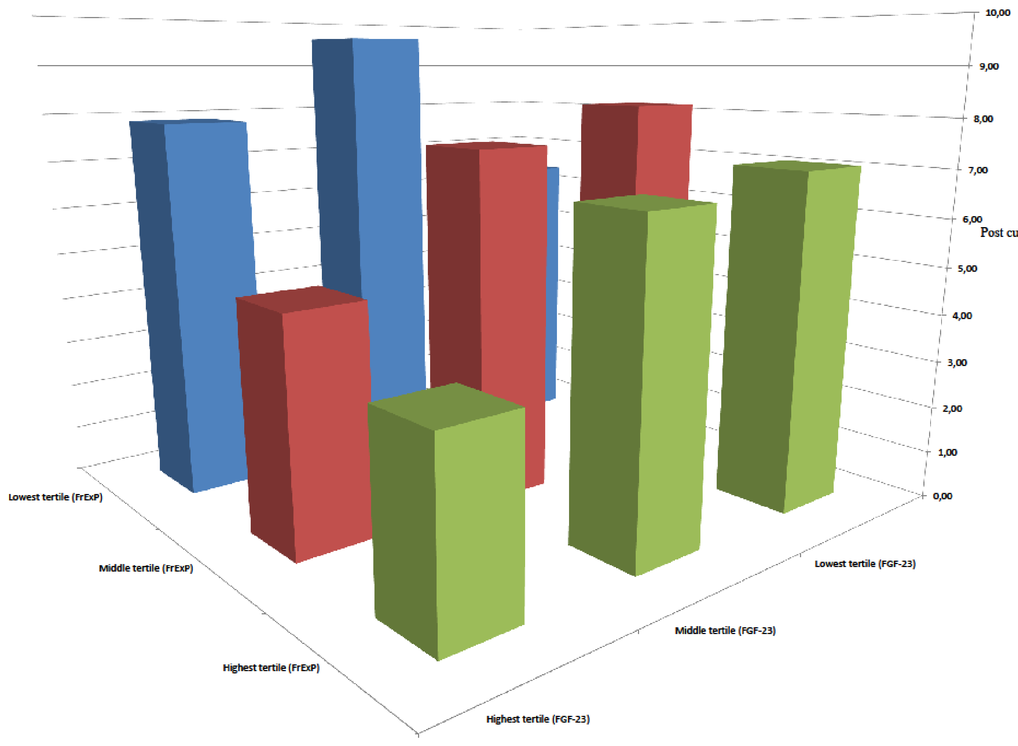

Figure 3: Relationship between fractional excretion of phosphate and FGF23 with post cuff FMD

4. Conclusions

1. This is the first study to demonstrate that sustained phosphate loa endothelial function.
2. The observed deleterious effect on FMD seen with PS may be ex elevated total body phosphate with resultant elevated intra-cellula
3. Elevated FeP and FGF-23 are likely to be surrogate markers of hi body phosphate.
4. Urinary cGMP, as a marker of endothelial dysfunction negatively with serum phosphate level.
5. This study supports the hypothesis that phosphate increases cardi risk by impairing endothelial function, possibly via the nitric oxi
6. Sustained phosphate loading is directly detrimental to the vascula when serum phosphate remains within the normal range.