Fibroblast Growth Factor 23 correlates with aortic valve calcifications and non-dipper status in chronic kidney disease patients

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Background

- Fibroblast growth factor 23 (FGF-23) is a circulating phosphaturic hormone that is elevated in patients with chronic kidney disease (CKD) and is strongly associated with mortality and cardiovascular disease [1-5]
- Previous studies showed that FGF-23 induces left ventricular hypertrophy via FGFR-dependent, but klotho-independent, effects on cardiac myocytes,[6] while some data suggest that FGF-23 is not associated with and does not induce arterial calcification [7]
- Elevated FGF-23 levels in CKD may also contribute to other forms of subclinical cardiovascular injury

Aim of the study

The aim of the present study is to determine whether there is an association between FGF-23 with respect to aortic valve calcifications, arterial stiffness and dipping status in CKD patients

Methods

- We enrolled **54 subjects**: 44 CKD patients (8 patients in CKD stage 2, 24 patients in CKD stage 3, 12 patients in CKD stage 4) in whom we performed complete evaluation, and 10 healthy controls in whom we performed peripheral pulse wave analysis and we determined markers of inflammation and mineral metabolism
- **FGF-23, IL-6, TNFα** and **iPTH** were evaluated using xMAP technology (Luminex® 200™)
- All patients underwent **24 h ambulatory blood pressure monitoring** (ABPM); we recorded mean systolic and diastolic blood pressure, and dipper status
- **Peripheral pulse wave analysis** was performed using SphygmoCor device; we recorded pulse wave velocity (PWV), augmentation index (Aix), left ventricular ejection duration index (EjD%, ratio of the duration of systolic ejection to the total duration of a cardiac cycle), subendocardial viability ratio (SEVR% = DTPI/STPI, diastolic pressure time index divided by systolic pressure time index)
- **Echocardiography** 2D and M-mode was used to assess the presence of aortic valve calcifications and left ventricular hypertrophy

RESULTS

Markers of inflammation and mineral metabolism

- Levels of FGF-23, IL-6 and TNFα and were significantly higher ($p<0.05$) in CKD patients compared to healthy controls

	CKD patients	Controls	*p*
FGF-23 (pg/mL)	106.84 ± 134.26	9.49 ± 0.79	***0.001***
IL-6 (pg/mL)	7.09 ± 4.56	1.05 ± 0.42	***0.002***
TNFα (pg/mL)	6.82 ± 6.45	1.33 ± 0.51	***0.001***

- Levels of FGF-23, IL-6 and TNF-alpha inversely correlated with eGFR
- FGF-23 significantly correlate with markers of inflammation and mineral metabolism (TNFα, p=0.01; IL6, p=0.0001; iPTH, p=0.01) and proteinuria (p=0.008)

FGF-23	iPTH	IL6	TNFα	Hb	serum albumin	eGFR	Ca	PO4	proteinuria
Pearson Correlation	0.489	0.818	0.519	-0.391	-0.316	-0.538	-0.063	0.354	0.491
Significance (2-tailed)	***0.010***	***0.000***	***0.01***	***0.040***	***0.163***	***0.004***	***0.761***	***0.106***	***0.008***

Ambulatory blood pressure monitoring

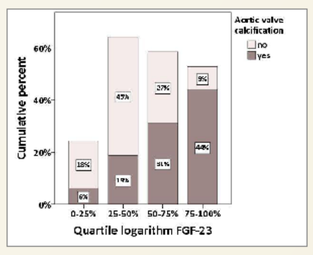
- Non-dipper pattern was identified in 54.4% CKD patients
- FGF-23 and IL-6 were significantly increased ($p<0.05$) in CKD patients with non-dipper versus dipper pattern

	Dipper pattern	Non-dipper pattern	*p*
eGFR (ml/min/1,73m²)	44.1 ± 16.8	32.7 ± 14.5	***< 0.05***
Proteinuria (g/day)	0.25 ± 0.41	0.35 ± 0.83	***NS***
Calcemia (mg/dl)	9.4 ± 0.9	9.3 ± 0.6	***NS***
Phosphatemia (mg/dl)	3.6 ± 0.5	3.7 ± 0.8	***NS***
iPTH (pg/ml)	73.5 ± 59.9	79.3 ± 59.3	***NS***
FGF-23 (pg/mL)	52.3 ± 42.1	175.7 ± 180.9	***< 0.05***
IL-6 (pg/mL)	5.5 ± 2.6	8.8 ± 5.7	***< 0.05***
TNF (pg/mL)	4.1 ± 4.6	7.7 ± 6.9	***NS***

RESULTS

Aortic valve calcifications

- Calcifications of aortic valve were present in 58.2% CKD patients
- Percent of patients presenting with aortic valve calcifications was greater in patients with increased levels of FGF-23 (as divided in quartiles after logarithmic transformation)

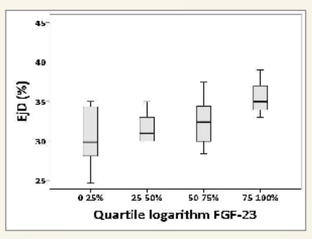


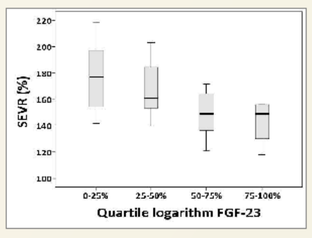
- Presence of aortic valve calcifications was significantly correlated with eGFR, FGF-23 and TNFα

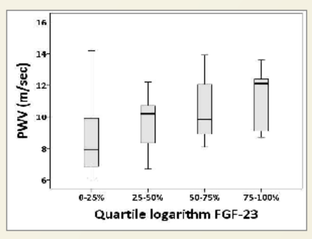
Aortic valve calcifications	FGF23	iPTH	IL6	TNFα	Hb	serum albumin	eGFR	Ca	PO4	proteinuria
Spearman`s rho	0.406	0.252	0.086	0.466	-0.104	-0.206	-0.412	-0.028	0.153	0.303
Significance (2-tailed)	***0.01***	***0.205***	***0.663***	***0.015***	***0.598***	***0.371***	***0.008***	***0.893***	***0.497***	***0.125***

Peripheral pulse wave analysis

- As levels of FGF-23 increased (upper quartiles of lnFGF-23), PWV and EjD increased, and SEVR decreased







- FGF-23 correlated with ED and SEVR, but not with AiX and PWV

FGF-23	PWV	EjD	SEVR	AiX
Pearson Correlation	0.444	0.523	-0.519	0.187
Significance (2-tailed)	***0.118***	***0.02***	***0.019***	***0.359***

Discussions

- In our study we noticed that increased levels of FGF-23 in CKD patients are associated with non-dipper pattern of blood pressure, although did not correlate with arterial stiffness as measured by PWV
- Although previous data showed that FGF-23 is not associated with vascular calcification, we found a correlation with presence of aortic valve calcifications
- Higher levels of FGF-23 in CKD correlate with markers of subclinical ventricular impairment, by means of prolonged ejection duration and decreased "supply versus demand" ratio as expression of subendocardial ischemia

Conclusions

Our results suggest a link between FGF-23 and presence of valvular calcifications (aortic valve), left ventricular function (evaluated by EjD and SEVR) and non-dipper status in chronic kidney disease patients. Further studies are necessary to determine if FGF-23 contributes to direct injury of cardiovascular structure and function.

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