Vascular effects of FGF-23 in hemodialysis patients

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Background: FGF-23 levels rise progressively in renal failure. FGF-23 associated vascular toxicity is currently investigated.

Patients & Methods: In 81 hemodialysis (HD) patients we measured levels of c-terminal FGF-23 (cFGF-23) and intact FGF-23 (iFGF-23) by ELISA, common carotid intima-media thickness (ccIMT) by ultrasound, and carotid to femoral pulse wave velocity (cfPWV) by applanation tonometry and simultaneous ECG recording (SphygmoCor©, AtCor Medical, Australia).

Patients were stabilized on maintenance hemodialysis for more than three months, on a thrice weekly schedule with synthetic dialyzers and bicarbonate dialysate of 1.0 -1.5 mmol/L Ca++ concentration. Patients with active infection, malignancy, liver disease, on immunosuppressive therapy or a history of parathyroidectomy were excluded. Serum samples were taken before a midweek dialysis session and measurements were done on a day between two sessions within a month from serum sampling. Patients gave their informed consent for inclusion to the study, which was approved by our institution's ethical committee.

Statistical analysis was done on the SPSS® v13.0 software. Normality of distribution of continuous variables was tested with the K-S test. Nonlinear variables were log-transformed before entering the analysis. Associations between continuous variables were tested with Pearson's correlation test and multi-linear regression. Differences between categorical variables were tested with the independent samples t-test, one way ANOVA and logistic regression. A two-tailed p value of <0.05 was considered statistically significant.

Results: Patients' main epidemiological characteristics and laboratory results are summarized in **Table 1.**

Levels of ***iFGF-23*** (mean log10 SD 2.61 0.41) and ***cFGF-23*** (3.51 0.52) were high and as a continuous variable correlated strongly with each other (p<0.001, r=0.798), with Kt/V (p=0.009, r=-0.289 and p=0.003, r=-0.327 respectively), phosphorus levels (p=0.003, r=0.323 and p=0.000, r=0.397) Ca x P product (p=0.000, r=0.387 and p=0.000, r=0.453), iPTH levels (p=0.001, r=0.348 and p=0.001, r=0.368), HDL (p=0.021, r=-0.26 and p=0.001, r=-0.361) and triglycerides (p=0.026, r=0.249 and p=0.043, r=0.052). iFGF23 levels were higher in smokers (p=0.005 95%CI=-0.46 to -0.08). There was no association with diabetes, coronary heart disease (CHD), ccIMT or cfPWV. In a multi-linear adjusted model only phosphorus levels remained significantly associated with iFGF23 (p=0.018) and cFGF23 (p=0.013).

ccIMT was associated with age (p=0.000), the presence of diabetes (p=0.005) or CHD (p=0.001), CRP levels (p=0.02) and cfPWV (p<0.001). In a multi-linear regression model age was the only independent predictor of ccIMT (p=0.000).

cfPWV was associated with age (p<0.001), the presence of hypertension (p=0.024), diabetes (p=0.039) or CHD (p=0.016), levels of LDL (p=0.037) and ccIMT (p<0.001). In multi-linear regression only age (p=0.034) and the presence of hypertension (p=0.038) retained an independent association with cfPWV.

Higher than the mean levels of iFGF-23 but not cFGF-23 were associated with higher ccIMT (p=0.03, 95% CI= -0.15 to -0,01) (**Fig.1**). This association was independent of serology (p=0.03) but was lost after controlling for the presence of diabetes (p=0.077) and CHD (p=0.053).

In a subgroup of 59 patients without CHD a PWV<9m/s vs ≥11m/s was associated with higher iFGF-23 levels (p=0.01, 95% CI= -0.6 to -0.9) (**Fig.2**). This was independent of age, smoking status, presence of diabetes and levels of phosphorous and iPTH (p=0.042).

Table 1. Basic epidemiological, and laboratory parameters of 81 HD patients

Age, *(years)*	59.8 15.7	Phosphorus (mg/dl)	5.2 1.4
Male	52 (64.2)	Ca x P (mg^2/dl^2)	46.4 13.1
Duration of dialysis *(months)*	66.2 53.9	iPTH (pg/dl)	359 276
		APL (IU/l)	94 39.8
Diabetes	17 (21)	Albumin (g/dl)	4.0 0.3
Hypertension	57 (70.4)	Cholesterol (mg/dl)	150.2 38.5
		LDL (mg/dl)	73.8 31.7
CHD	22 (27.2)	HDL (mg/dl)	44.9 14.1
Smoker	25 (30.9)	Triglycerides (mg/dl)	139.7 63.6
Statin	29 (35.8)	Hb (g/dl)	11.3 1.2
SHPTH Treatment	61 (75.3)	CRP (mg/l)	7.2 9.3
Kt/ V	1.46 0.21	cfPWV (m/s)	9.91 2.29
Urea (mg/dl)	132.7 32.8	ccIMT (mm)	0.833 0.166
Creatinine (mg/dl)	9.3 2.1	*log*iFGF-23	2.61 0.41
Calcium (mg/dl)	8.7 0.7	*log*cFGF-23	3.51 0.52

Values are expressed as mean SD, and number of patients (%) as appropriate, ALP: Alkaline Phosphatase, CHD, Coronary Heart Disease, CRP: C-Reactive Protein, ccIMT: common carotid Intima – Media Thickness, LDL: Low Density Lipoprotein, cfPWV: carotid femoral Pulse Wave Velocity, SHPTH: Secondary Hyperparathyroidism

Figure 1.

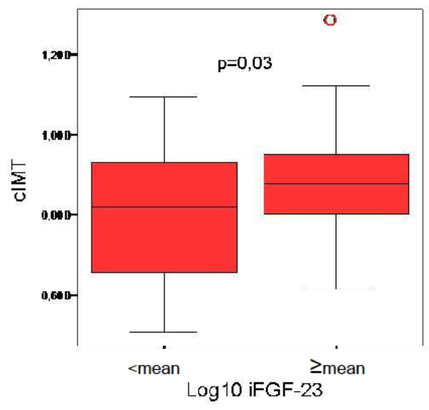
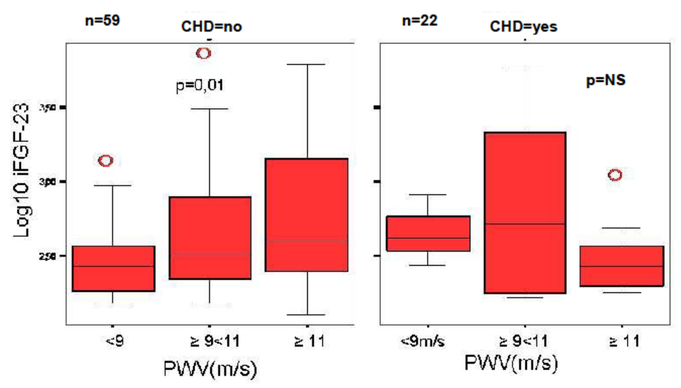


Figure 2.



Discussion: FGF-23 has been associated left ventricular hypertrophy, atherosclerosis and endothelial dysfunction in experimental models (1,2) and in patients with reduced renal function (3-6). We tried to investigate associations of FGF-23 levels, both intact and c-terminal, with cardiovascular pathology in hemodialysis patients.

Study limitations include a cross-sectional design, precluding proof of causality, and sample size, affecting statistical power.

Nevertheless higher iFGF-23 levels were associated with higher cIMT as already described in hemodialysis patients (7), even though not independently of the presence of diabetes or CHD, probably due to power limitations of our study. Our results describe also a novel independent association of iFGF-23 with higher PWV in HD patients without CHD, implying a potential association with early vascular toxicity.

FGF-23 is renaly excreted and its levels rise with progressive loss or glomerular filtration rate (8). Although considered equally representative with levels of the intact molecule, FGF-23 fragments tend to accumulate in HD (9). Therefore iFGF-23 might prove more sensitive in revealing potential associations in this setting. In our study associations regarded levels of iFGF-23 rather than cFGF-23.

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