KLOTHO, BUT NOT FGF-23, IS ASSOCIATED WITH ATHEROSCLEROTIC VASCULAR CHANGES IN CHRONIC HAEMODIALYSIS PATIENTS

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OBJECTIVES

Recent evidence suggest that Klotho and FGF-23 may have a role in inducing vascular dysfunction and promoting cardiovascular morbidity and mortality in chronic kidney disease patients. The aim of this study was to investigate the probable association between the above factors and the extent of both arteriosclerotic and atherosclerotic vascular changes in chronic haemodialysis (HD) patients.

METHODS

Eighty-one (81) chronic HD patients entered the study. In all patients common carotid artery intima-media thickness (cIMT) and carotid–femoral pulse wave velocity (cfPWV) were measured, as markers of atherosclerosis and arteriosclerosis respectively. cIMT was measured by ultrasonography, using a high resolution B-mode 10MHz transducer (Aloka© Prosound A6) and cfPWV was estimated using an applanation tonometry transducer (SphygmoCor©). Plasma Klotho (sklotho), intact FGF-23 (iFGF-23) and C-terminal FGF-23 (cFGF-23) levels were determined by a two site second-generation sandwich ELISA using commercially available standard kits [human soluble α-Klotho (Immuno-Biological Laboratories Co, Fujioka-Shi Japan) and human intact FGF-23 και human C-term FGF-23 (Immutopics Inc, San Clemente, California USA) respectively].

RESULTS

Demographic and laboratory data of the study population (n=81) are depicted in Table 1.

iFGF-23 and cFGF-23 plasma levels showed a significant positive correlation with serum phosphate ($p<0.0001$ for both), the Ca x P product ($p<0.0001$ for both) and iPTH levels ($p=0.004$ and $p=0.009$ respectively) and a significant negative correlation with Kt/V ($p=0.002$ and $p=0.003$ respectively) and HDL-cholesterol levels ($p=0.016$ and $p<0.0001$ respectively). No association was observed between iFGF-23 and cFGF-23 with either cIMT or cfPWV values.

sKlotho levels had an inverse correlation with age ($p=0.043$) (Fig.1) and serum CRP values ($p=0.046$) and a significant positive correlation with HDL-cholesterol serum levels ($p=0.004$). Patients with coronary artery disease (CAD) had significantly lower sklotho levels than patients without CAD ($p=0.006$) and as a result patients with CVD [coronary artery disease (n=22), cerebrovascular disease (n=6) or peripheral occlusive vascular disease (n=9)], had lower serum sklotho levels than patients without CVD ($p=0.045$). Moreover, a strong negative correlation was observed between cIMT values and sKlotho levels ($p=0.001$) (Fig.1). This association remained significant after adjustment for traditional and uremia-related CVD risk factors (Table 2). No correlation was observed between sklotho levels and cfPWV.

Table 1. Clinical characteristics and biochemical assessments of the study population, expressed as number of patients and percentage, mean±SD or as median and range

Age (years)	59.8 ± 15.7	**Diastolic BP (DBP)(mmHg)**	83.6 ± 12.1	**Albumin (g/dl)**	4.0 ± 0.3
Male n(%)	52 (64.2)	**Mean BP (MBP)(mmHg)**	100.9 ± 13.4	**CRP (mg/L)**	7.2 ± 9.3
Time on dialysis (months)	66.2 ± 53.9	**Cholesterol (mg/dl)**	150.2 ± 38.5	**Hemoglobin (g/dl)**	11.3 ± 1.2
Kt/v	1.46 ±0.21	**Triglycerides (mg/dl)**	139.7 ± 63.6	**cFGF-23 (pg/ml)**	2820 (370.7 – 50964.5)
Smoking n(%)	25 (30.9)	**Serum calcium (mg/dl)**	8.7 ± 0.7	**iFGF-23 (pg/ml)**	317 (127 – 7244.4)
Diabetes n(%)	17 (21)	**Serum phosphate (mg/dl)**	5.2 ± 1.4	**sKlotho (pg/ml)**	222.8 (117– 620)
Hypertension n(%)	57 (70.4)	**iPTH (pg/ml)**	359 ± 276	**cfPWV (m/sec)**	9.9 ± 2.3 (6.2 – 16.1)
CVD n(%)	30 (37)	**Urea (mg/dl)**	132.7±32.8	**cIMT (mm)**	0.8 ± 0.2 (0.5 – 1.3)

Figure 1. Significant associations of sklotho in the study population

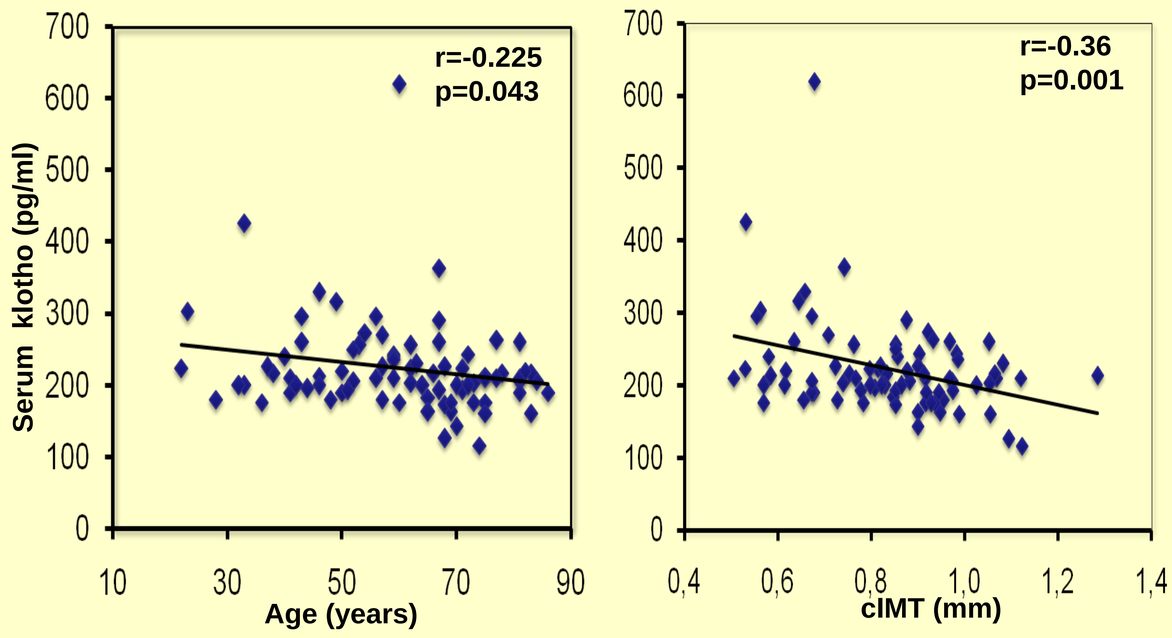

Table 2.Multiple regression analysis of factors that affect cIMT

Parameter	β	SE	t	p
Constant	0.578	0.130	4.438	<0.0001
Age	0.61	0.001	6.35	<0.0001
Diabetes	0.11	0.03	1.46	0.14
CVD	0.11	0.02	1.41	0.16
DBP	0.009	0.003	0.38	0.97
MBP	-0.11	0.003	-0.48	0.63
logCRP	0.01	0.04	0.17	0.86
sklotho	-0.15	0.0001	-2.08	0.04
cfPWV	0.081	0.007	0.83	0.40

CONCLUSIONS

We report for the first time a significant association of circulating sklotho with the presence of atherosclerosis in dialysis patients.

Neither iFGF-23 nor cFGF-23 plasma levels correlated with cfPWV or cIMT.

The observation that sklotho in our patients had a strong association with HDL cholesterol serum levels, would indicate that in addition to its other functions, sklotho could influence lipid metabolism and consequently regulate the atherosclerotic process.

sklotho levels had a weak inverse association with CRP serum levels, suggesting that reduction of sklotho might induce inflammatory responses.

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Dialysis. Cardiovascular complications.

Panagiotis Giamalis

DOI: 10.3252/pso.eu.53era.2016

ePosters supported by F. Hoffmann- La Roche Ltd.

53rd CONGRESS ERA-EDTA VIENNA AUSTRIA MAY 21st-24th, 2016 Held jointly with Österreichische Gesellschaft für Nephrologie

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