Role of Morphogenetic Proteins - FGF-23, Klotho and glycoprotein Sclerostin in Vascular Calcification in Chronic Kidney Disease Patients


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The aim of the study was to investigate the relationship between FGF-23, Klotho, Sclerostin serum concentration changes and diffuse arterial calcification intensity in the patients with different stages of Chronic Kidney Disease (CKD).

Materials and Methods: 65 patients with CKD 1-5D stage were included in the study: 25 - with chronic glomerulonephritis, 20 - tubulointerstitial nephritis 20 - hypertensive nephrosclerosis (33 men and 32 women, 20-65 years old, mean age at enrollment was 41 ± 6.7 years). The control group consisted of 15 volunteers the same average age and sex. Serum FGF-23 levels (Human FGF-23 ELISA kit using monoclonal antibodies to the full FGF-23 molecule), Klotho (Human alpha-Kl ELISA using anti-Klotho antibodies) and Sclerostin (Human Sclerostin ELISA kit) were applied in these patients. Blood pressure (BP) was measured in all study patients. Echocardiography was performed to patients with arterial hypertension and left ventricular mass index (LVMI) was calculated. The state of blood flow in the heart and large vessels (Doppler ultrasound Echocardiography), pulse wave velocity (Sphygmokor), calcifications presence (echocardiography, radiography of abdominal aorta by Kauppila method) and vascular wall functional ability (augmentation indices by Sphygmokor) were studied. Among 49 hypertensive patients in 29 (59.1%) from them it was able to maintain target BP-130/80-140/80 mm Hg., the remaining 20 (40.7%) patients took antihypertensive medications irregularly. At the start of screening they remained hypertensive (BP 150/90-165/100 mm Hg.).

Results: A strong direct correlation \([r=0.731, p<0.01]\) was established between stage of CKD by MDRD and serum FGF-23 concentration, inverse correlations \([r= -0.489, p <0.01]\) and \([r= -0.510, p<0.01]\) were established between stage of CKD and Klotho and stage of CKD and Sclerostin concentrations respectively. When comparing serum FGF-23 levels in patients with different CKD stages was found FGF-23 levels increases with decreasing GFR ahead of serum phosphorus and PTH levels elevating, starting at CKD 3a stage, whereas hyperphosphatemia and increased PTH levels were started in CKD-4 -5 stage. At the same time, Klotho and Sclerostin serum concentrations reducing in patients with CKD progression were in inverse correlation with serum levels of phosphorus and PTH. We assessed the serum morphogenetic proteins changes depending on BP levels. The degree of increasing blood pressure correlated positively with FGF-23 serum concentrations \((r = 0.452; p <0.01)\) and inversely with Klotho concentrations \((r = -0.687; p <0.01)\). Significant correlation of the sklerostin levels with the degree of hypertension has not been received. In addition, it was found the feedback between enhanced FGF-23 levels with increased left ventricular mass \((r = 0.452; p <0.05)\). In hypertensive patients \((n = 20)\) this connection was extremely expressed \((r = 0.850 p<0.05)\). We also established the strong straight relationship of FGF-23 serum concentrations \([r =0.492, p<0.01]\) and the reverse relationship of serum Klotho levels \([r = -0.537; p<0.01]\) and Sclerostin serum levels \([r =-0.541, p<0.05]\) respectively with time of pulse valve reflection (Sphygmokor). In studied patients reduced serum Klotho and Sclerostin levels have been clearly associated with a higher frequency of stiffness and calcificat identification in the heart valves (Echocardiography) \([\text{mitral valve} r=-0.492 p<0.01 \text{ and } r= 0.487 p<0.01, \text{respectively}]\) and large arteries (abdominal aorta) \([\text{Kloto} r =-0.525,p<0.01]\).
These correlations were strongest in the hypertensive patients who failed to achieve an adequate blood pressure correction (n = 27). Reduced serum Klotho and Sclerostin levels have been also associated with a concentric remodeling of the myocardium \([r = -0.445 \ p<0.01 \text{ and } r = -0.567 \ p<0.01]\).

**Conclusion.** It was found the clear link between increased serum FGF-23 and decreased Klotho as increasing CKD severity, and diffuse arterial stiffness and calcification, myocardial remodelling independent of traditional risk factors. To clarify the role of Sklerostin more exactly further researches are required.