Summary

Chronic kidney disease (CKD) is a long-term disorder associated with multisystem organ dysfunctions, resulting from the permanent damage or progressive loss of active nephrons. The incidence of CKD is increasing due to population aging and the widespread coexistence of cardiovascular and metabolic diseases. It is estimated that in Poland it affects approximately 12-18% of the population. However, this calculation is probably underestimated due to incomplete reporting and delay in diagnosing early stages of the disease. Although CKD is a progressive and irreversible disease, early diagnosis and adequate treatment can slow its progression. Common background, including oxidative stress, chronic subclinical inflammation, and accumulation of macromolecular damage in post-mitotic cells are involved in the pathogenesis of CKD, cardiovascular diseases, and the aging process. Therefore, it is warranted to investigate novel biomarkers of CKD and cardiovascular risk, including a better understanding of proteins originally known as 'longevity gene' products, which overexpression were associated with increased lifespan in animal models.

Sirtuin 1 is an enzyme responsible for post-translational modification of proteins and epigenetic regulation of gene expression depending on the energy state of the cell. It is involved in the pathogenesis of several age-related diseases, for which it exhibits protective properties, by regulating responses to oxidative stress, inflammation, mitochondrial function, apoptosis, lipid, and carbohydrate metabolism. In the human body, α-klotho protein is predominantly expressed in renal tubules, where it acts as a transmembrane protein, being a coreceptor for the FGF23 protein, thus it is involved in the regulation of calcium-phosphate metabolism. The second form is secretory one which regulates ion transport, renin-angiotensin-aldosterone system, inflammation, kidney fibrosis and have antiaging properties.

The aim of the study included in this doctoral dissertation was to assess the serum concentration of sirtuin 1 and α-klotho in patients with stable CKD depending on the estimated GFR based on the creatinine and cystatin C concentration; to analyze the relationship between the studied proteins and other parameters of kidney function; to establish the relationship between their concentration and selected laboratory parameters, coexistence of cardiovascular diseases, demographic factors, and the impact of systemic treatment.

The study included 100 adults with CKD, not requiring renal replacement therapy, and 24 healthy volunteers. Clinical data were collected on the basis of medical history, physical examination and the results of laboratory tests carried out using standard methods in a hospital laboratory, available in the CliniNet computer system. Serum sirtuin 1, α-klotho and cystatin C

determinations were performed using commercial enzyme immunoassays according to the manufacturer's instructions.

Serum sirtuin 1 concentration was significantly higher in the studied group compared with the control group ($p<0.0001$). A considerable increase in the median sirtuin 1 concentration between stage 1 CKD and control group was noted. Further gradual increase across CKD stages was accompanied by greater range of concentrations in particular subgroups. Sirtuin 1 significantly correlated with conventional CKD biomarkers and eGFR equations, with the strongest association with CKD-EPI cystatin C formula ($R = 0.61$, $p<0.001$). It was demonstrated that sirtuin 1 can distinguish CKD from the control group (cut-off: 0.96 ng/mL) with high sensitivity and specificity (93% and 87%, respectively; AUC = 0.954, 95% CI 0.919–0.989). A positive correlation with iPTH level ($R = 0.39$, $p<0.001$) and age ($R = 0.27$, $p = 0.002$) was found. Retrospective evaluation of pharmacotherapy revealed that statins, AT1 receptor antagonists and β-blockers use was associated with decreased sirtuin 1 concentration. In the multiple regression analysis only iPTH concentration (beta = 0.3, $p = 0.009$) was an independent predictor of sirtuin 1 level. No relationship was found between terciles of sirtuin 1 concentration and death outcomes.

The concentration of α-klotho protein was higher in the control group than in the group of patients with CKD ($p>0.05$). As the disease progressed, a gradual decrease in the concentration of the investigated protein was observed, and its concentration was significantly lower in the group of patients with moderate and severe impairment of renal function compared to patients with mild impairment and normal eGFR ($p <0.05$). The α-klotho protein was correlated with conventional CKD markers and the eGFR. Moreover, a statistically significant negative correlation between α-klotho and age, BMI, uric acid, and triglyceride levels was found. Serum α-klotho concentration was not related to treatment, comorbidities and had no effect on survival over the 24-month follow-up period.

Conclusions:

1. The serum sirtuin 1 concentration in CKD patients is considerable increased compared to heathy subjects.
2. Sirtuin 1 concentration can discriminate, with high sensitivity and specificity, CKD patients and healthy subjects, thus it may serve as novel biomarker of impaired kidney function.
3. The accumulation of serum sirtuin 1 may be related to decreased kidney function.
4. A strong association between sirtuin 1 and iPTH concentration suggests the usefulness of sirtuin 1 as kidney function or indirectly cardiovascular risk biomarker.

5. In terms of iPTH being the only independent predictor of serum sirtuin 1 concentration, it may be considered as cardiovascular risk biomarker, regardless of renal function.

6. Sirtuin 1 has cardio- and nephroprotective properties, thus the increased sirtuin 1 concentration may be a compensatory mechanism to decreased protein activity.

7. Alternatively, a positive correlation between sirtuin 1 and iPTH, may be related to accumulation of (7-84) - PTH having opposite biological effects to full-length PTH.

8. The serum α-klotho concentration correlates with kidney function impairment but is not sufficiently sensitive marker of the disease.

9. The decreased α-klotho concentration may be a marker of the metabolic syndrome and increased cardiovascular risk in patients with CKD.