Chronic kidney disease (CKD) is a global health problem of 21st century affecting 12-15% of the world population. Nowadays, about 4.5 million Polish people suffer from kidney diseases, and about 36 million people in the European Union have CKD in stages III-IV without awareness of its progression. Mineral and bone disorders that accompany CKD are known as CKD-MBD (Chronic Kidney Disease – Mineral and Bone Disorders). CKD-MBD are connected with increased risk for spontaneous bone fracture, which in turn leads to significant deterioration in quality of life, and increase in morbidity and mortality of patients with CKD.

Due to the complexity of process, causes of CKD-MBD still arouse much controversy. A significant role is attributed to the accumulation of toxic metabolites – uremic toxins, which is a result of impaired renal function. Indoxyl sulfate (IS) is one of aggressive uremic toxins with complex mechanism of action. Its serum and tissue levels in patients with CKD can be even 80 times higher compared to healthy subjects. Moreover, the implementation of renal replacement therapy – hemodialysis or peritoneal dialysis – results in a reduction of IS concentration in only about 30%.

IS has a multidirectional effect on the body. Its accumulation leads to numerous metabolic and structural disorders in the course of CKD-MBD. Significant abnormality is the contribution of IS in the calcification of blood vessels and loss of muscle mass, which limits mobility of the joints and thus increases the risk of falls of patients with CKD. Moreover, recent studies indicate that IS suppresses the differentiation and activation of osteoblasts and osteoclasts in cell cultures. However, the current state of knowledge concerning IS impact on bone structure does not provide complete information.

The aim of this project is to evaluate IS as an indirect and direct factor responsible for disorders of bone homeostasis.

Experiments proposed in this study include comprehensive assessment of the IS effects on bone and mineral disorders in CKD. We are going to use two animal models for this purpose. The first is a model of CKD induced by chronic administration of nephrotoxic compound – adenine. This model leads to accumulation of the endogenous IS. In the second model, IS will be chronically administered to healthy rats in doses corresponding to the serum IS concentrations achieved in patients with impaired renal function. Bone structure will be evaluated in detail in both models. Geometric, biomechanical and morphometric parameters will also be assessed. Besides, IS impact on bone mineralization, calcium-phosphate metabolism and bone turnover will be determined. Moreover, the evaluation of AhR gene expression in bone tissue will allow us to try to evaluate the connection between IS and AhR receptors, which have negative impact on the geometry and biomechanical properties of the bone.

Undoubtedly, the integration of biomechanics, analytical chemistry, molecular biology, biochemistry and biostatistics will provide results to allow a full assessment of the IS effects on metabolic processes and biomechanical properties of bone, and to define the role of IS in the CKD-MBD. The obtained data can provide the basis for development of new direction of pharmacotherapy of mineral and bone disorders in CKD patients, and thereby contribute to improved quality of life of these patients.