**Summary**

Abnormalities in bone metabolism, classified as chronic kidney disease mineral and bone disorders (CKD-MBD), are common systemic disorders accompanying the development of CKD. They lead to morbidity, mortality, increased the risk of fractures, and significantly decreased the quality of CKD patients' life. In recent years, reports indicated that serotonin and kynurenine, belonging to products of tryptophan metabolism, may play an important role in the development of CKD-MBD. The researchers proved that both serotonin and kynurenine released peripherally to circulation could inhibit the activity of osteoblasts and bone formation processes. Additionally, the kynurenine leads to an increase in the activity of osteoclasts and intensification of bone resorption processes by activation of the aryl hydrocarbon receptor. It has been also proved that the progression of CKD is accompanied by an accumulation of both of these compounds, which results in the deterioration of bone biomechanical and geometric parameters. LP533401 is an inhibitor of tryptophan hydroxylase-1 (TPH-1), an enzyme responsible for the synthesis of peripheral serotonin. Previously we found that inhibition of TPH-1 by LP533401 decreases a plasma serotonin concentration and may improve bone mineralization in rats with experimentally induced CKD. The effect of inhibition of peripheral serotonin synthesis on the kynurenine pathway activity remained unexplained.

This doctoral dissertation aimed to establish, whether the bone tissue possesses its own kynurenic system and evaluate its potential effect on bone metabolism, as well as to assess if the inhibition of serotonin synthesis by LP533401 may affect kynurenine pathway activity in bone tissue of nephrectomized rats and to determine the background and potential consequence of this process in relation to osteogenesis and regulation of bone mineral status.

Nephrectomized rats were randomized into: untreated, treated with a vehicle, and treated with LP533401 at a dose of 30 and 100 mg/kg daily for 8 weeks. Tryptophan and kynurenine concentrations were determined using high-performance liquid chromatography. The expression level of tryptophan 2,3-dioxygenase (TDO) was assessed using the quantitative real-time polymerase chain reaction method.

The results of my research demonstrated for the first time the presence of a TDO-dependent paracrine kynurenic system, occurring in the bone tissue of CKD rats, functioning regardless of the peripheral one. Inhibition of peripheral serotonin synthesis by LP533401 may indirectly modulate the activity of this pathway. The observed changes in its activity were associated with impaired bone mineral status. The changes in TDO expression level affecting the kynurenine pathway activity in the bone tissue of the LP533401-treated animals were related to the imbalance between peripheral serotonin and 25-hydroxyvitamin D levels. There were also close associations between the expression of genes that participated in osteoblastogenesis, particularly with osteoblast maturation markers, and TDO-dependent activation of the kynurenine pathway in the bone tissue of CKD rats treated with LP533401.

Although it is not yet possible to match all the data presented in this dissertation to the simple mechanistic hypothesis of the progression of osteoporosis in CKD, the obtained results represent the next step in studying the role of tryptophan metabolites in the development of renal osteodystrophy. They also provide the basis for further research on the role of the kynurenine pathway in the development of CKD and the modulation of its activity in the course of renal failure.