Summary

Monitoring of bone metabolism affected by selected drugs

Osteoporosis is one of the most common metabolic bone diseases, which belong to civilization diseases, and is a major health and socioeconomic problem, particularly in the older age groups. Cardiovascular diseases are one of the great problems of our society and a leading cause of death worldwide. The major risk factors include hypercholesterolemia and arterial hypertension, which can be effectively reduced by several groups of drugs. At the present, not much attention has been paid to whether or how these drugs affect bone metabolism. With increasing age, people are more likely to develop hypertension and hypercholesterolemia with progressive loss of bone leading to osteoporosis. Many studies have suggested that antihypertensive and hypolipidemic drugs in some way influence bone metabolism.

The subject of the present thesis was to investigate the effect of selected, frequently prescribed antihypertensive drugs (amlodipine, metoprolol), and hypolipidemic drugs (ezetimibe, atorvastatin) on bone metabolism in healthy male Wistar albino rats and in rats after orchidectomy (Wistar and spontaneously hypertensive rats).

During my postgradual study, three experiments in rats with above mentioned drugs were performed. In the first experiment, drugs (metoprolol, amlodipine, atorvastatin, ezetimibe, a combination of amlodipine + atorvastatin) were administered to male albino Wistar rats with bone metabolism undisturbed castration. In the second study, drugs (amlodipine, metoprolol, atorvastatin) were administered to orchidectomized Wistar rats. In the third experiment, orchidectomized spontaneously hypertensive rats were treated with antihypertensive drugs (amlodipine, metoprolol).

Ezetimibe did not show any significant effect on bone metabolism in healthy male rats. Other drugs caused suppression of bone turnover and increased synthesis of osteoblast growth factor BMP-2 in bone tissue. After administration of metoprolol, maximum strength of the right femoral neck was increased. Results from the left femur were not significant, but showed a reduction of the femoral neck maximum load.

Orchidectomy induced acceleration of bone turnover as indicated by increased concentrations of bone markers, reduction of IGF-I, bone mineral density and increased fragility of the femur. Suppression of bone turnover by decrease in bone markers and increase in IGF-I were shown after 12 weeks administration of drugs to orchidectomized Wistar rats. The most effective agent seems to be atorvastatin, which increased bone mineral density, diameter and length of the femurs, and thus improved bone strength compared with orchidectomized control rats. Furthermore, amlodipine improved whole-body bone mineral density and parameters of the left femur (diameter, thickness of cortical bone and the maximal strength of the femoral shaft). In the right femur, the values had the same tendency, but were not significantly changed.

In the third experiment, antihypertensive drugs were given to orchidectomized spontaneously hypertensive rats for 12 weeks. Amlodipine and metoprolol caused a suppression of bone turnover, which had been increased by the influence of orchidectomy. The antihypertensive drugs did not have statistically significant effects on the bone mineral density and mechanical properties of bone tissue.

Obtained data allowed demonstrating the effect of selected drugs on bone metabolism. Ezetimibe, a selective cholesterol absorption inhibitor, had no effect on bone metabolism in rats. Atorvastatin, an inhibitor of cholesterol synthesis, showed the most positive effect on bone tissue. Statins exhibit many pleiotropic effects, which include also effect on bone metabolism, which was demonstrated in the presented work. It can be assumed that atorvastatin has a very positive effect on the skeleton, at least in rats. Another drug that appears to be beneficial on bone metabolism is the calcium channel blocker amlodipine. β-blocker metoprolol has inconsistent effects on bone tissue, especially in the compression test of the femoral neck. The maximal load was decreased in healthy male Wistar rats, but in orchidectomized rats this negative effect was not demonstrated.

It can be assumed that the dihydropyridine derivatives and statins could delay the symptoms of osteoporosis, at least in rats. It is necessary to perform further experiments using more modern instrumentation and molecular biology methods. It is also necessary to confirm the effect on the skeleton in retrospective or prospective studies in patients taking these drugs.