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Fund “Nauka” Project № 18017 Resume – Competition-Based Session 2018:
“Comparative characteristics of metabolic markers in postmenopausal women with osteopenia and osteoporosis”
Project leader: Prof. Kiril Hristov Hristozov, MD, PhD

Objective: To establish a link between bone health in postmenopausal women and their metabolic profile by comparing some metabolic parameters and inflammatory markers and to evaluate the effects of different components of the metabolic syndrome on bone health.

Tasks:

1. Assessment of bone health in postmenopausal women by performing osteodensitometry at the level of lumbar spine and thighs, as well as examination of markers of bone metabolism.
2. Evaluation and analysis of anthropometric, hormonal, metabolic and inflammatory parameters that could be related to the deteriorating bone health of postmenopausal women.
3. Assessment and analysis of the influence of blood pressure and intake of antihypertensive drugs on bone health.
4. Evaluation of the effects of the metabolic syndrome on bone health and establishment of complex connections between the studied parameters of the metabolic profile and bone health.
5. Determining a risk profile for compromised bone health in postmenopausal age.

Materials and methods: the subject of the study are postmenopausal women with data on a missing menstrual cycle of ≥1 years. The assessment of bone health includes examination of bone mineral density at the level of proximal femur and lumbar spine by dual-energy X-ray absorptiometry, as well as calculation of fracture risk. Evaluation of markers of bone metabolism (osteocalcin, alkaline phosphatase, Beta-crosslaps, pyrylinks D/ creatinuria), levels of vitamin D, serum calcium and serum phosphorus are also considered. To rule out thyroid and parathyroid dysfunction, an analysis of thyroid-stimulating hormone and parathyroid hormone is planned. Clinical examination should determine: height, weight, waist circumference and mean blood pressure value. The evaluation and analysis of metabolic parameters should specify the state of carbohydrate, lipid metabolism and uric acid levels. An assessment of the proinflammatory condition includes CRP and TNF-alpha assay.

Hypotheses:

1. Older age and longer duration of menopause are leading determinants of impaired bone health in postmenopausal women.
2. Higher body weight is likely to counteract excessive bone loss in postmenopausal women.
3. Carbohydrate and lipid metabolism parameters could be additional determinants of bone health in postmenopausal women.
4. Hypertension and especially poor control blood pressure are likely to be an additional risk factor for bone health in postmenopausal women.
5. The different number and degree of manifestation of each component within the metabolic syndrome, as well as the approach to their compensation, probably determine the complex relationship between the metabolic syndrome and the bone.

Expected results:

The onset of menopause and old age are known as leading non-modifiable risk factors for the development of osteoporosis in women. However, it is known that there are additional determinants of bone health that can be corrected and thus supporting the prevention, prophylaxis and treatment of osteoporosis. The role of obesity on bone health, for example, can be combined. Due to the higher body weight and the associated mechanical load on the skeleton, positive effects on the bone could be manifested. On the other hand, the abnormal accumulation of visceral adipose tissue in obesity can reduce and neutralize these benefits. However, unbalanced weight loss in obesity could also adversely affect bones. It is also suggested that the role of insulin in bone health may be complex. This statement is supported, on the one hand, by the hypothesis of the osteoanabolic action of insulin and the view that peripheral resistance to insulin hypoglycaemic action is not necessarily accompanied by insulin resistance at the skeletal level. In addition, hyperinsulinemia adversely affects the binding of sex hormones to SHBG and therefore leads to increased levels of free sex steroids, which play a key role in achieving and maintaining higher bone mass. On the other hand, insulin resistance and linked hyperinsulinemia are associated with atherogenic dyslipidemia, low-grade inflammation and increased oxidative stress, which can adversely affect bone. Some relationships have also been established between bone health in postmenopausal women and lipid metabolism. Analysis of the effect of lipid parameters on the skeleton is likely to be associated with a divergent effect of atherogenic dyslipidemia. There is a wealth of evidence for the adverse effects of hypertension on bone health. It is assumed that the negative relationship between arterial hypertension and bone is determined not only by elevated blood pressure, but

also by the stage of hypertension. On the other hand, we believe that maintaining optimal blood pressure values and properly selected antihypertensive therapy, if necessary, could support the prevention, prophylaxis and treatment of osteoporosis. In fact, the various components of the metabolic syndrome could affect bone health in different directions. The different number and degree of manifestation of each component within the syndrome, as well as the approach to their compensation, probably determine the complex relationship between the metabolic syndrome and the bone. In this regard, the project team suggests that the metabolic syndrome may not be a significant risk factor for postmenopausal osteoporosis.

Achieved results:

As a result of the project, the possible relationships of the metabolic syndrome and its components with bone health in postmenopausal women were analyzed.

After analysis of the evaluated clinical, laboratory and imaging parameters it was found that:

1. Primary postmenopausal osteoporosis is associated with an increased bone metabolism, in which bone formation falls behind bone resorption;
2. The serum bone resorption marker Beta Crosslaps is a more informative indicator of osteoclast activity, while the pyrilinks D/ creatinine ratio in urine is modulated by extraosseous factors affecting glomerular filtration;
3. Age and duration of menopause are leading non-modifiable risk factors for deterioration of bone health in postmenopausal age;
4. Optimal levels of 25(OH)D and calcium-phosphorus balance are preconditions for better bone integrity in postmenopausal women;
5. Body weight is associated with better parameters of bone integrity, but this relationship could be counterbalanced by obesity;
6. Higher basal insulin levels with preserved insulin sensitivity are associated with better bone integrity, while insulin resistance and concomitant hyperinsulinemia are associated with deteriorating bone health in postmenopausal age;
7. The relationship between lipid metabolism and bone health could be divergent, probably determined by the degree of deviation in different lipid parameters;
8. The proinflammatory cytokine TNF alfa negatively correlates with bone integrity, while the inflammatory marker CRP is not associated with changes in bone health in the postmenopausal period;
9. The negative association of arterial hypertension with bone health in postmenopausal age is determined by the maintenance of higher diastolic blood pressure, the lack of timely initialed antihypertensive therapy and the stage of arterial hypertension;

10. The complex relationship between metabolic syndrome and bone health depends on the number, combination and degree of manifestation of the individual components of the syndrome.

Contribution:

1. Based on the obtained results, a risk profile for compromised bone health in postmenopausal age has been determined.
2. According to the identified additional determinants of bone health in postmenopausal age, a comprehensive analysis of the cardio-metabolic profile in the assessment of bone integrity is recommended.
3. In addition, recommendations are given for non-drug and drug correction of the identified additional risk factors in order to more comprehensive prevention, prophylaxis and treatment of osteoporosis, as well as to avoid adverse skeletal effects associated with the treatment of comorbidities.

The project supported by the Science Fund at MU-Varna is part of a dissertation for awarding an educational and scientific degree “PhD” to Dr. Radina Stoyanova Dimitrova on topic “Comparative characteristics of metabolic markers in assessment of postmenopausal bone health”. An original article is also published on topic “Postmenopausal bone health may be influenced by the presence of arterial hypertension and antihypertensive therapy”; Scripta Scientifica Medica, Medical University of Varna, 2021.