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Fund “Nauka” Project № 17001 Resume – Competitive-based Session 2017:

“The impact of vitamin K-dependent protein osteocalcin on the regulation of the energy metabolism in women with metabolic syndrome”

Project leader: Assoc. prof. Maria Delcheva Zhelyazkova-Savova, MD, PhD

Osteocalcin (OC) is a bone-specific vitamin K-dependent protein existsing in two major forms – carboxylated (cOC) and uncarboxylated (ucOC). Vitamin K is responsible for OC carboxylation and its intake increases the levels of cOC. The ratio ucOC/cOC is considered a marker of the vitamin K status in the body. Whilst the role of OC in bone is currently unsettled, recent information has accumulated favoring a hormonal activity of OC as a stimulator of insulin secretion and sensitivity. In experimental animals the evidence identifies the ucOC as the hormonally active form, but in humans the data are equivocal. Many clinical trials, looking for a connection between osteocalcin levels and parameters of the energy metabolism in healthy persons or patients, report generally negative correlations with blood glucose and beneficial changes in insulin sensitivity. Such correlations, however, have been found not only for ucCO, but also for cOC and total OC. On the other hand, epidemiological studies show that vitamin K intake improves glycemic control and reduces insulin resistance and decreases the risk of type 2 diabetes.

The objective of the current project is to establish whether body weight reduction in female patients with metabolic syndrome will be accompanied by changes in osteocalcin forms and if yes, will they correlated with laboratory measures of energy metabolism.

The study will include 40 women with metabolic syndrome aged 18-50 years, who will be subjected to 30 days dieting procedure aiming at reduction of body weight in a specialized clinic. Routine clinical and biochemical parameters characterizing the glucose and lipid homeostasis will be followed up. The serum levels of cOC and ucOC will be measured at the beginning and at the end of the dieting program. In case a dynamics is found in these levels, correlations will be sought with the clinico-laboratory measures.

We expect that this study will throw some light on questions in the field still unclarified: What is the role of osteocalcin in metabolic syndrome in humas? Which is the active hormonal form of osteocalcin in humans? Is there a connection between the clinical improvement of women with metabolic syndrome and potential changes in osteocalcin levels?

Results:

The results of the project revealed that both carboxylated and uncarboxylated osteocalcin were reduced in patients with type 2 diabetes compared to non-diabetic controls. The results were in agreement with the hypothesis that this bone-derived protein is involved in

the regulation of energy metabolism. As expected, vitamin K2 supplementation increased the serum levels of the carboxylated osteocalcin. The concentration of the uncarboxylated protein was not significantly changed. The correlation analysis revealed that carboxylated osteocalcin was associated with several parameters of energy homeostasis. It was negatively correlated with the anthropometric parameters of general and visceral obesity (body mass index, waist circumference and waist-to-height ratio) and positively correlated with HDL-cholesterol in the entire sample and in the non-diabetic group. In the diabetic group, carboxylated osteocalcin was similarly associated with waist circumference and HDL-cholesterol. Uncarboxylated osteocalcin was negatively correlated only with fasting blood glucose level in the non-diabetic group.

No differences in the level of oxidative stress were found between the two groups. Correlation analysis also did not reveal any relationship between osteocalcin levels and oxidative stress.

The project results showed that osteocalcin levels were related to the parameters of energy metabolism indicating involvement in its regulation. We found beneficial metabolic associations for both forms of osteocalcin, the carboxylated being more active.

As vitamin K2 supplementation increased the serum levels of carboxylated osteocalcin, we might conclude that, through this mechanism, it could have beneficial effects on energy metabolism in patients with type 2 diabetes.

The project results were presented in two full-text scientific publications and a poster presentation at an international scientific forum.