THE ROLE OF AMYLIN IN THE DEVELOPMENT OF DIABETIC OSTEOPATHY

Teacher of public health technical college named after Republic No. 1 Abu Ali Ibn Sina
Tuxtayeva Muborak

Annotation: *Diabetes mellitus adversely affects the bone. Basically, it is related to weakening of the anabolic effect of insulin and other pancreatic hormones. Mechanisms underlying the decrease in bone density are not fully understood. However, many of the systemic changes related to metabolic abnormalities in diabetes have a damaging effect on the bone tissue. Inadequate compensation of glycemic profile in this disease, both directly (non-enzymatic glycosylation of proteins, activation of polyol pathway of glucose metabolism, oxidative stress) and indirectly (violation of gene expression), damages the bone structure. Another anabolic hormone produced by β-cells of the pancreas is amylin. It is a potent hypoglycemic and antiresorptive hormone affecting calcium homeostasis and influencing the preservation of bone density. The studies have shown that amylin, on the one hand, stimulates osteoblast proliferation, and on the other hand, inhibits osteoclast motility, thus acting similar to calcitonin. Inefficient redistribution of bone mass occurs. This may explain the increased incidence of fractures in patients with type 2 diabetes on the background of high bone density according to densitometry. In this regard, further studies are required to clarify the effect of amylin deficiency on the development of osteoporosis.*

Keywords: *amylin, bone mineral density, diabetes mellitus, bone fractures.*

Diabetes mellitus (DM) is a common metabolic disease. Population growth and aging, lifestyle characterized by low physical activity, and consumption of high-calorie foods contribute to an increase in the number of patients with DM. Chronic complications of DM negatively affect organs and systems, including bones, and are a heavy medical and social burden. Typical bone complications in poorly compensated DM include diabetic foot syndrome and Charcot's neuropathy, which account for a high percentage of surgical procedures, including amputations. Fractures associated with low bone strength are increasingly recognized as a consequence of diabetic complications. In patients with type 1 DM, which manifested itself in adolescence or young age, bone tissue does not reach peak mass, bone formation is impaired, which becomes a fundamental factor in the development of osteopenia. In patients with type 2 DM, bone mineral density may remain high. In particular, in type 2 diabetes, there is a positive relationship between insulin levels and bone mineral density, but this does not protect against fractures, since the quality of bone tissue deteriorates. The

mechanisms underlying the decrease in bone strength are not fully understood. At the same time, many of the systemic changes associated with metabolic disorders in diabetes have a damaging effect on bone tissue. Thus, unsatisfactory compensation of the glycemic profile in diabetes both directly (non-enzymatic glycosylation of proteins, activation of the polyol pathway of glucose metabolism, oxidative stress) and indirectly (impaired gene expression) has a damaging effect on bone structure. The interaction of advanced glycation products with bone cell receptors causes inflammatory reactions, the accumulation of non-enzymatic cross-oxidation products inside collagen fibers and increased free radical reactions negatively affect the properties of the bone matrix. This disrupts the collagen cross-links of the bone and can lead to structural changes in bone tissue. Considering the fact that the organic matrix of bone tissue consists of approximately 90% type I collagen and 5% type III–V collagen, bone tissue collagen undergoes non-enzymatic glycation processes, which results in disruption of the structure and functions of bone tissue, of which it is a component. These systemic changes can also directly and negatively affect the remodeling cycle and lead to a disruption of bone strength in diabetes. Thus, the existence of pathophysiological mechanisms linking pancreatic β-cell insufficiency with disruption of bone tissue formation is obvious. The impact of diabetes on the skeleton is associated, among other things, with the absence or weakening of the anabolic effect of insulin and other pancreatic hormones on bone. Physiologically, insulin has an anabolic effect on bone due to its structural homology with insulin-like growth factor-1 — by interacting with the receptor of this growth factor, which is present on osteoblasts. Insulin-like growth factor-1 stimulates osteoblastic osteopoiesis, bone matrix synthesis and ensures normal bone mineralization by stimulating collagen synthesis and amino acid transport into bone. Insulin deficiency leads to osteoclast activation and increased catabolic processes in the bone matrix by affecting mesenchymal differentiation of stem cells and osteoblastogenesis.

Another anabolic hormone that stimulates osteoblast proliferation is amylin (AMY). It is a secretory product of pancreatic and brain β-cells with structural and functional similarities to calcitonin. This review examines the known effects of AMY on the regulation of a number of processes in the body. Thus, AMY plays an important role in the physiological regulation of glycemia and energy balance management. It improves postprandial blood glucose levels by suppressing gastric emptying and glucagon secretion. AMY also acts on satiety centers, reducing food intake and body weight. In addition to these more widely studied effects, a growing body of literature suggests that AMY may play a role in processes related to bone metabolism. Although the functions of AMY are not completely understood, recent reports suggest that AMY may positively influence osteogenesis. AMY affects bone formation by stimulating osteoblast proliferation and decreasing biochemical markers of osteoresorption, resulting in increased levels of biochemical markers of osteogenesis. High serum

AMY levels correlate with high bone mass density. AMY acts as a growth factor that stimulates osteoblast proliferation, enhances the effect of osteocalcitonin in long tubular bones, and normalizes trabecular bone structure. AMY also has an osteoclast-inhibiting effect. AMY deficiency increases osteoclast activity, leading to osteopenia. The effect of AMY on bone tissue is associated with its effect on osteoblast-osteoclast differentiation. Studies on the potential effects of AMY on bone density have shown the prevalence of osteopenia in patients with diabetes. Indeed, this effect of AMY is one of the main physiological effects described since its discovery. AMY has been shown to act as a bone growth factor, participating in osteoblast proliferation, and more recently its role in osteoclast differentiation has been identified.

AMY acts early in embryonic development [8], suggesting its role as a physiological growth factor. Studies have shown that AMY has profound hypoglycemic and osteoclast inhibitory effects in humans. AMY has also been shown to have 30-fold less activity than calcitonin. Subsequently, AMY has been shown to act as a growth factor, stimulating osteoblast proliferation and osteoclast differentiation in humans. The opposite effects on bone formation and resorption suggest that AMY acts through two distinct sets of receptors, the first located on osteoclasts (possibly CTR RAMP1 or CTR RAMP3) and the second on osteoblasts.

AMY stimulates osteoblast cell proliferation approximately 10-fold. Deamination of AMY and reduction of its concentration act in the opposite way. AMY acts on osteoblasts by stimulating the formation of cyclic adenosine monophosphate (cAMP) and activating mitogen-active protein kinase and protein kinase-C. Thus, a number of studies have confirmed that AMY inhibits bone resorption and suppresses osteoclastogenesis by stimulating cAMP. This is due to cAMP-dependent inhibition of osteoclast mobility (Q-effect), which is a consequence of gradual retraction of pseudopodia (R-effect), which reduces the contact of osteoclasts with the bone surface. Q- and R-effects on osteoblasts are indirectly stimulated by G-protein. Osteoclasts are multinucleated cells that are formed from bone marrow stem cells (macrophages) and migrate to the bone through the vessels. AMY inhibits osteoclast mobility (Q-effect), thus acting similarly to calcitonin, but less pronounced. It has been shown that the effect of AMY on bone resorption is similar to the effect of calcitonin, but AMY only partially repeats the effect of calcitonin on osteoclasts. Accordingly, this suggests that the effect of AMY can be mediated through the effect on osteoclast activity and is a consequence of the release of the enzyme. Activation of osteoclasts requires the participation of ions Ca2+, phosphates, K+, Mg2+, Na+, the concentration of which AMY also affects. In this regard, AMY may be responsible for the suppression of osteoclast activity, which until now was associated exclusively with calcitonin. The data obtained indicate ineffective redistribution of bone mass in type 2 diabetes. This may explain the inability to assess the increased risk of fractures in patients with type 2 diabetes mellitus with higher bone mineral density using

densitometry. In conclusion, it should be noted that AMY is a potent hypoglycemic and antiresorptive peptide that affects metabolic processes in bone tissue. Among the described effects of AMY, its effect on calcium homeostasis and its role in maintaining bone density are important. Reduced clearance of AMY in diabetes mellitus indicates the importance of including it in the spectrum of determined parameters for studying the state of bone tissue. Given the clinical significance of AMY, further studies on its effect on bone tissue are advisable to understand the mechanisms of bone complications in diabetes mellitus.

REFERENCES:

1.ZhukouskayaV.V., Eller-VainicherC., Vadzianava V.V. et al. Prevalence of morphometric vertebral fractures in patients with type 1 diabetes. Diabetes Care. 2013; 36 (6): 1635–1640. DOI: 10.2337/dc12-1355.

2. Leslie W.D., Aubry-Rozier B., Lamy O., Hans D. Bone density program. TBS (trabecular bone score) and diabetes-related fracture risk. J. Clin. Endocrinol. Metab. 2013; 98 (2): 602–609. DOI: 10.1210/jc.2012-3118.

3. Johnston S.S., Conner C., Aagren M. et al. Association between hypoglycaemic events and fallrelated fractures in Medicare-covered patients with type2 diabetes. Diabetes Obes. Metab. 2012; 14 (7): 634–643. DOI: 10.1111/j.1463-1326.2012.01583.x.

4. Napoli N., Strotmeyer E.S., Ensrud K.E. et al. Fracture risk in diabetic elderly men: the MrOS study. Diabetologia. 2014; 57 (10): 2057–2065. DOI: 10.1007/s00125-014-3289-6.