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The role of amylin in the development of diabetic osteopathy

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Abstract

Diabetes mellitus (DM) adversely affects bone health, because of the weakening of the anabolic effect of insulin and other pancreatic hormones. However, the mechanisms underlying the decrease in bone density are not fully understood. However, many of the systemic changes related to metabolic abnormalities in DM have a damaging effect on bone tissues. The inadequate compensation of glycemic profile characteristic of this disease, both directly (through nonenzymatic glycosylation of proteins, activation of polyol pathway of glucose metabolism, and oxidative stress) and indirectly (through violation of gene expression), damages the bone structure. Another anabolic hormone produced by pancreatic β cells is amylin. It is a potent hypoglycemic and antiresorptive hormone that affects calcium homeostasis and influences the preservation of bone density. Studies have shown that amylin stimulates osteoblast proliferation and inhibits osteoclast motility, thereby acting similar to calcitonin. Inefficient redistribution of bone mass occurs. This may explain the increased incidence of fractures in patients with type 2 DM who appear to have a high bone density according to densitometry. 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.

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Diabetes mellitus (DM) is a common metabolic disease. Growth and aging of the population, and the modern lifestyle, characterized by low levels of physical activity and consumption of high-calorie foods, have contributed to an increase in the number of patients with DM.

Chronic complications of DM have adverse effects on various organs and systems, including the skeletal system, and are a serious medical and social burden. Typical bone complications in poorly managed DM include diabetic foot syndrome and Charcot arthropathy, which account for a high percentage of surgical procedures, including, in the most severe cases, amputations [1]. Fractures associated with low bone strength are increasingly recognized as one of thecomplications of DM [2].

In patients with type 1 DM, manifested in adolescence or young age, bone tissue does not reach the peak weight and bone formation is disrupted, which becomes a fundamental factor in the development of osteopenia [3]. In patients with type 2 DM, bone mineral density may remain high. In particular, type 2 DM, there is a positive correlation between the level of insulin and bone mineral density, but this does provide protection against fractures due to deterioration in the quality of bone tissue [4].

The mechanisms underlying the reduction in the strength of bone tissue are not fully understood. At the same time, many of the systemic changes related to metabolic disorders in DM have a damaging effect on bone tissue [5]. Thus, unsatisfactory management of the glycemia in DM has a damaging influence on bone structure, both directly (through nonenzymatic glycosylation of proteins, activation of the polyol glucose metabolism pathway, and oxidative stress) and indirectly (through violation of gene expression) [6].

The interaction of the final glycation products with bone cell receptors causes inflammatory reactions, accumulation of the products of nonenzymatic cross-oxidation inside collagen fibers, and enhancement of free-radical reactions [7], thus adversely affecting the properties of bone tissue matrix [8]. This breaks the collagen bone cross-links and can lead to structural changes in bone tissue.

Considering that approximately 90% of the organic matrix of bone tissue is composed of type I collagen, with the remainder being composed of collagen types III, IV, and V [9], the collagen of bone tissue undergoes nonenzymatic glycation processes, and the structure and function of bone tissue is disturbed as a result [10]. These systemic changes can also have a direct adverse effect on the cycle of bone remodeling and lead to reductions in the strength of bone tissue in DM.

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Thus, pathophysiological mechanisms between insufficient pancreatic β cells and disruption in the formation of bone tissue is evident. The effect of DM on the skeleton is caused by the lack or weakening of the anabolic action of insulin and other pancreatic hormones on the bone [1].

Physiologically, insulin has an anabolic effect on the bones because of its structural homology with insulin-like growth factor-1 [11, 12] and its interaction with the receptor of this growth factor that is present on osteoblasts [7, 13]. Insulin-like growth factor-1 stimulates osteoblastic osteopoiesis and bone matrix synthesis and ensures normal bone mineralization by stimulating collagen synthesis and bringing amino acids into bone [14, 15]. Insulin deficiency leads to the activation of osteoclasts and the enhancement of catabolic processes in the bone matrix by affecting the mesenchymal differentiation of stem cells and osteoblastogenesis [16].

Another anabolic hormone that stimulates the proliferation of osteoblasts is amylin (AMY) [17]. It is secreted by β cells of the pancreas and brain and is structurally and functionally similar to calcitonin [18]. In this review, the already known effects of AMY on the regulation of a number of processes in the body are considered.

AMY plays an important role in the physiological regulation of glycemia and maintenance of energy balance. It improves postprandial glucose levels in the blood by suppressing the evacuation function of the stomach and secreting glucagon [19]. AMY also acts upon saturation centers, thereby reducing food intake and body weight [14]. In addition to these more widely studied effects, a growing volume of literature suggests that AMY could have a role in the processes associated with the metabolism of bone tissues [20]. Although the functions of AMY are not fully understood, recent reports indicate that AMY can positively influence osteogenesis [21].

AMY affects the formation of bone tissue, stimulating the proliferation of osteoblasts and reducing the number of biochemical markers of osteoresorption, leading to an increase in the content of biochemical markers of osteogenesis [22]. High blood serum levels of AMY correlate with high bone mass density. AMY functions as a growth factor, stimulating the proliferation of osteoblasts, enhancing the effect of osteocalcitonin in long tubular bones, and normalizing the structure of the trabecular bone [23]. AMY also has an osteoclastoinhibitory effect [24]. In cases of AMY deficiency, osteoclast activity is increased, which leads to osteopenia [13].

The effect of AMY on bone tissue is associated with its effect on the differentiation of osteoblasts and osteoclasts. Studies on the potential effect of AMY on bone density indicate a prevalence of osteopenia in patients with DM [22]. Indeed, this effect is one of the main physiological effects of AMY that has been described since its discovery. AMY has been demonstrated to act as a bone growth factor participating in proliferation of osteoblasts [25], and its role in the differentiation of osteoclasts was recently revealed [18].

The effect of AMY is manifested at the beginning of embryonic development [8], and its involvement as a physiological growth factor has been suggested [19, 24, 26]. Studies indicate that AMY has a strong hypoglycemic effect and that it inhibits osteoclasts in humans [20]. It has also been found that the activity of AMY is 30-fold lower than that of calcitonin [15]. Subsequently, it was proved that AMY acts as a growth factor that stimulates the proliferation of osteoblasts [6] and differentiates osteoclasts in humans [22].

The opposing effects that AMY has on the formation and resorption of bone tissue assumes that it acts by means of two different receptor groups, the first of which is located on osteoclasts (possibly CTR·RAMP1 or CTR·RAMP3) and the other on osteoblasts [27]. AMY stimulates the cellular proliferation of osteoblasts by approximately 10 times [28]. The deaminization of AMY and the decrease in its concentration act conversely. AMY influences osteoblasts by stimulating the formation of cyclic adenosine monophosphate (cAMP) and activating mitogen-active protein kinase and protein kinase-C [9]. Thus, a number of studies confirmed that AMY, by stimulating cAMP, inhibits bone resorption and suppresses osteoclastogenesis [20]. This is due to cAMP-dependent inhibition of osteoclast mobility (Q effect), which is a consequence of the gradual retraction of pseudopodia (R effect) and the consequent reduction in the contact between osteoclasts and bone surface. Q and R effects on osteoblasts are mediated by G-protein stimulation [16].

Osteoclasts are multinucleated cells that are generated in bone marrow stem cells (macrophages) and migrate to bone through blood vessels [9]. AMY inhibits the mobility of osteoclasts (Q effect) [16], thereby acting similarly to calcitonin, but with a less pronounced

effect. It has been found that the AMY effect on bone resorption is similar to that of calcitonin, but AMY only partially replicates 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 enzyme release [20]. The activation of osteoclasts requires the participation of Ca^{2+} ions, phosphates, K^{+}, Mg^{2+}, and Na^{+} [13], whose concentrations are also influenced by AMY. In this regard, AMY may be responsible for osteoclast activity inhibition, which until now has been associated solely with calcitonin [26].

Data indicate that the redistribution of bone mass in patients with type 2 DM is ineffective [10]. This could explain the inability to assess by densitometry an increased risk of fracture in patients with type 2 DM with high levels of bone mineral density.

In conclusion, it should be pointed out that AMY serves as 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 role in the maintenance of bone density are important. The reduced clearance of AMY in DM [25] indicates the significance of including it in the spectrum of determined indicators for studying the condition of bone tissue. Given the clinical importance of AMY, it is advisable to perform further studies to analyze its effect on bone tissue, in order to understand the mechanisms behind the development of bone-related complications in DM.

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