

The Endocrine Functions of Bone

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Editorial

Received date: 15/01/2017

Accepted date: 16/01/2017

Published date: 22/01/2017

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Keywords: Glucose metabolism, Energy metabolism, Osteocalcin, Insulin, Osteoblast, Bone.

INTRODUCTION

Until a few years ago, it was thought that the bone was simply a support and protection structure. Then, it was discovered that bone also served as a hematopoietic niche and for calcium homeostasis. Nevertheless, recent breakthroughs in bone science have shown that the skeleton also has true endocrine roles^[1-3]. This was demonstrated by the presence of novel hormones produced by bone cells that control mineral ion homeostasis and energy balance. An example of these hormones is a hormone called fibroblast growth factor 23 (FGF23), which is synthesized by the osteocytes^[1]. This hormone regulates serum phosphate levels by altering levels of active vitamin D and the activity of specific phosphates transporters in the kidney, providing an additional layer of control to aid parathyroid hormone in the maintenance of phosphate levels during bone resorption. This hormone also regulates 1-alpha-hydroxylase and parathyroid hormone. Also, osteocalcin has been linked to FGF23; they are produced exclusively in bone and have endocrine functions through regulatory loops subject to both feedforward and feedback control^[1,3,4].

Another hormone is osteocalcin; this is produced by osteocytes and osteoblasts under the control of insulin and this hormone increases the efficiency of glucose utilization through its actions on the pancreas and adipocytes^[4,5]. Studies have shown that there is an association between osteocalcin and glucose metabolism. Osteocalcin levels are significantly lower in diabetic patients, and the levels of this hormone are increased with improved glycemic control^[2,6]. Osteocalcin may also have another hormonal role, as a mediator of testosterone secretion. It has been shown that osteocalcin can induce testosterone production in leydig cells of the testes through a novel G protein-coupled receptor (GPCR6A) that is expressed on the surface of leydig cells^[1,7].

Furthermore, maternally derived osteocalcin crosses the placenta, reaches the developing brain and favors hippocampal development. In the adult brain, osteocalcin crosses the blood-brain barrier, regulated the synthesis of various neurotransmitters, prevents anxiety and favors spatial learning and memory^[1].

It is known that osteoblasts –the building cells of bone– express functional insulin receptors and respond to exogenous insulin by increasing bone anabolic markers, including collagen synthesis, alkaline phosphatase production and glucose uptake^[8]. Localized insulin delivery accelerates bone healing in osteopenia and osteoporosis models by enhancing osteogenesis. This could explain why patients with type 1 diabetes mellitus can develop early-onset osteopenia or osteoporosis and have an increased risk of fragility fracture^[9]. There are several other regulators implicated in the endocrine functions of bone, such as vitamin D, gastric inhibitory polypeptide (GIP), adiponectin, osteoprotegerin, among others. These molecules play a role in osteoclastogenesis, glucose metabolism and energy metabolism. Their specific functions are beginning to be demonstrated, but further research needs to be performed^[8].

Bone morphogenetic proteins (BMPs) are a group of growth factors and have a critical role in embryogenesis, bone and cartilage formation and function. These proteins are frequently used in orthopedic surgery for the management of bone grafting and non-unions^[6]. The roles of BMPs in adipogenesis and energy metabolism have recently been described. It has been shown that BMPs have roles in adipocyte development, adipocyte cell fate determination, differentiation of committed preadipocytes

and function of mature adipocytes. Also, recent results have demonstrated that BMPs play a role in white adipocytes, during the “browning” of these cells. BMP 4 can regulate insulin sensitivity by affecting white adipocyte development ^[6].

Bone also participates in the global energy balance. This was shown when it was described that fat-derived leptin altered bone mass through a hypothalamic-osteoblast endocrine loop ^[9]. Interestingly, sphingolipids, which are a large class of lipid molecules containing a sphingoid backbone and until recently considered structurally inert, have been shown to be implicated in osteoblast and chondrocyte apoptosis and in the regulation of osteoclastogenesis ^[6].

The bone is an extremely complex organ and it is implicated in many physiological processes in the body. The recognition of bone as an endocrine organ represents an exciting area for further research and should improve the diagnosis and treatment of some metabolic diseases such as diabetes mellitus, obesity and osteoporosis. Development of new drugs to target the skeleton should be considered in order to treat metabolic diseases. In addition, due to the great size of the skeleton and to the huge amount of hormones and proteins involved with this organ, it is reasonable to think that there are still multiple roles of the bone to be discovered.

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