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Editorial

Estrogen Deficiency and Bone Remodeling

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Editorial

Bone is a dynamic tissue, lying in a constant process of remodeling [1]. Bone remodeling plays a fundamental role in the homeostasis of calcium serum levels [2]. In post-menopausal osteoporosis, resorption is increased when comparing to bone apposition. Consequently there is bone loss [3].

The mechanisms linking estrogen and the regulation of bone remodeling are still unknown [4], however, *in vitro* studies suggest that this hormone acts on secretion and activity of the factors that regulate osteoblast precursors and prevent osteoclast formation [5]. Estrogen receptors of osteoblasts and osteoclasts have regulatory functions in these cells and consequently in bone remodeling [1].

Osteoblasts exert their physiological signaling function mediating osteoclastic resorption when its activation occurs by inducers such as parathyroid hormone (PTH), interleukin 1 (IL-1), tumor necrosis factor (TNF) or prostaglandin (PGE-2), which stimulate osteoblasts to secrete factors that induce osteoclasts to resorb bone. The decrease in estrogen levels results in increased production cytokines involved in bone reabsorption [6].

Hughes et al. [7] investigated *in vitro* and *in vivo* the estrogenic function in the regulation of osteoclasts apoptosis. According to the authors, estrogen increases the production of TGF-β by osteoclasts. The anti-TGF-β antibody reduces apoptosis of osteoclasts. Thus, estrogens may regulate resorption, limiting osteoclasts life.

Estrogen has appreciable effect on the expression of cytokines and growth factors by osteoblasts and osteoclasts, which play an important role in itsparacrine and autocrine action. Some growth factors which can act in signaling, proliferation, migration and matrix synthesis by osteoblasts are: platelet derived growth factor (PDGF), insulin-like growth factors (IGF) I and II, fibroblast growth factor (FGF), transforming growth factor (TGF), especially TGF-ß and bone morphogenetic proteins (BMPs). Among these growth factors, the main related to estrogen are: IGF-I and II, TGF-ß and PDGF [8].

The IGF I and II can stimulate mitosis and collagen synthesis in osteoblasts, while TGF-ß displays dual effect, stimulating or depressing the osteogenic function. FGF and PDGF have similar functions, but with secondary importance.

The IGF also promotes the synthesis of cartilage matrix. Chondrocytes secrete IGF and reactto this factor in an autocrinesignaling pathway. Its role in bone remodeling and repair is not completely understood [9]. However, Okazaki et al. [10] believe that the inflammatory chemical mediators, such as prostaglandins, secreted after a trauma can induce the expression of IGF-I. In the early periods of repair, messenger ribonucleic acid (mRNA) of IGF-I was expressed by mesenchymal cells, immature chondrocytes, pre-osteoblasts, osteoblasts and osteocytes in bone callus. After two weeks of repair, osteoblasts continue to express IGF-I. This factor seems to be involved in the proliferation and differentiation of osteoblasts and chondrocytes, acting as an autocrine and paracrine mitogenic factor during bone repair.

Despite being found in lesser amounts compared to IGF-II, IGF-I promotes increased collagen synthesis, being more active on bone tissue [11].

With respect to the functions of TGF-beta, according Finkelman et al. [12] thedeficiency of thisfactor in ovariectomized ratsbone, suggest its importance in maintenance of bone volume, since it can induce proliferation and differentiation of bone cells [11].

Another route of action of estrogens on bone remodeling signaling is osteoprotegerin (OPG), receptor activator of NF-kB (RANK) and RANK cytokine ligand (RANKL), identified as the major factors involved in osteoclastogenesis. RANK is located on the surface of mature osteoclasts and their precursors, while RANKL is a protein that belongs to the tumor necrosis factor (TNF) family. Its main role is to inhibit apoptosis of osteoclasts and stimulate the differentiation and activation of these cells. OPG directly inhibit the binding RANKL with RANK.Its effects are antagonistic to the effects of RANKL.

Several cytokines and compounds such as estrogens affect osteoclastogenesis by regulating the production of RANKL/OPG by stromal cells and osteoblasts [13]. Subsequently menopause, bone loss arises because the RANKL action is favored above the OPG. Decrease of the estrogen levels reduces the OPG activity and improves the RANKL activity, resulting in increased resorption and bone loss.

Steeve et al. [13] reported that both estrogen and TGF-β increase OPG production, consequently decreasing the differentiation and activation of osteoclasts, as well as inducing apoptosis of these cells.

An experimental model that mimics estrogen deficiency in postmenopausal women is ovariectomy in rats, which results in decreased levels of estrogen [14]. As a result, ovariectomy causes bone loss. Despite differences between women and experimental animals, this model is considered appropriate to study osteopenia inestrogen deficiency [15]. An option is theexcision of testicles in male rats, but this type of study is less used than ovariectomy.

Avoid weight gain in ovariectomized animals is necessary because this, could be a protecting mechanism [16,17], which use the fat as a source of estrogenic hormones, and may alter bone loss desired in the study model sincebone, mammary glands, placenta and adipose

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tissue express the aromatase enzyme involved in the synthesis of estrogens [18]

New knowledge that can guide the therapeutic management of women with postmenopausal osteoporosis, can contribute in improving the quality of life of these patients. New studiesthat attempt to better understand the mechanisms of regulation of bone remodeling by estrogens areessential.

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