Molecular features of sexual steroids on cartilage and bone

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Summary

In Brazil, the increase in the reported cases of degenerative diseases of articular cartilage is 20% per year, meaning that 200,000 Brazilians develop degenerative joint diseases every year, which have a negative impact on bone mass. This study shows evidence that hormone production of sexual steroids (estrogens, progestogens, and androgens) have an influence on cartilage quality, as well as on bone mass. Therefore, this review aimed to analyze literature data on the molecular and genic action of sexual steroids on hyaline cartilage and bone physiology, as well as osteoarthritis interference on the quality of these structures.

Keywords: Sexual steroids; bone; hyaline cartilage; osteoarthritis.

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Bone formation

Bone formation occurs mainly during the embryo development and postnatal growth, being important in adults for bone remodeling and to maintain calcium homeostasis due to adaptation to physical forces. Bone formation requires recruitment, proliferation, and differentiation of osteoprogenitor cells[1].

Bone tissue is formed in two ways: one is an intramembranous process, and the other is endochondral. The process termed intramembranous occurs within a connective tissue membrane, and the endochondral process occurs on a hyaline cartilage model, which is gradually destroyed and substituted for bone tissue formed from the differentiation of cells in the adjacent connective tissue. Both in intramembranous and endochondral ossification, the first bone tissue formed is the primary type, which is slowly replaced with secondary, more resistant, bone tissue[2].

Long bone formation is endochondral, a more complex process than that occurring in other bones. From a cartilage model similar to the coming bone, a narrow middle part and wider ends are seen, corresponding, respectively, to the shaft and epiphyses of the mature bone. The first bone tissue found in a long bone is formed by intramembranous ossification of the cartilage model periphery at the perichondrium covering the mid-shaft, forming a cylinder, the bone collar. While the bone collar is formed, cartilage cells involved in the collar enlarge and die from apoptosis, leading to cartilage matrix mineralization. Blood vessels from the periosteum go through the bone cylinder and penetrate the calcified cartilage, taking along osteoprogenitor cells from the periosteum, which proliferate and differentiate into osteoblasts. These osteoblasts form a continuous cell layer on the surface of calcified cartilage partitions and initiate the synthesis of the bone matrix, that is soon mineralized. Primary bone tissue is thus formed on the remains of calcified cartilage[3].

The ossification center described above is seen at the mid-shaft, and it is called a primary center. Its longitudinal growth is fast and ends up occupying the whole shaft (diaphysis), that is then formed by bone tissue. This primary center spread is followed by the growth of the bone cylinder formed from the perichondrium, which also grows toward the epiphyses. Later on, secondary ossification centers are formed, one at each epiphysis, but not simultaneously, and radial growth takes place in these centers[2].

After epiphysis and diaphysis ossification, the remaining cartilages in the cartilage model of long bones are the articular cartilage and the epiphyseal plate. The articular cartilage will persist throughout life, and the epiphyseal plate cartilage, consisting of a cartilage disk that was not substituted for the expanding bone, will be responsible for the longitudinal bone growth and will disappear over time. This cartilage is found between the epiphysis and diaphysis bone tissue. It disappears approximately at the age of 20, when the longitudinal growth of long bones is arrested, thus causing arrest of growth[2,3].

Bone tissue is a specialized connective tissue presenting blood vessels, nerves, and cells (osteoblasts, osteocytes, and osteoclasts) which synthesize, reabsorb, and maintain the bone matrix (BM); these activities are under hormone influence[3,4]. Bone tissue formation involves, in addition to osteoprogenitor cells, a complex process, such as the apoptosis of cells present in the cartilage tissue (chondrocytes), which are replaced for bone tissue cells (osteoblasts and osteocytes). Bone remodeling takes place by sequential synthesis and breakdown of the bone matrix during its growth, which is performed by special cells (osteoblasts and osteoclasts, respectively)[2].

Hormones acting on cartilage and bone formation

Several factors act on bone cells during their differentiation, such as circulating molecules, hormones (parathyroid hormone – PTH, growth hormone – GH, progestogens, and androgens) or non-hormonal molecules (1,25 dihidrocholecalciferol, insulin-like growth factors types 1 and 2 – IGF 1 and 2), locally produced molecules with autocrine/paracrine action (IGF1 and 2, bone morphogenetic protein – BMP, prostaglandin E2 –PGE2, interleukin 1 – IL1, tumor necrosis factor α – TNF-α, granulocyte macrophage colony-stimulating factor – GM-CSH, transforming growth factor β – TGFβ, basic fibroblast growth factor 2 – BFGF2), and molecules present in the bone extracellular matrix (FGF2, TGFβ, GM-CSF, IGF1 and 2); they are inactive when bound to bone extracellular matrix (BEM) constituent molecules, but active on bone cells when BEM breakdown takes place. Quiescent osteoblasts regulate the osteoclast access, but under the action of bone-reabsorbing factors (PTH, dihidrocholecalciferol, and PGE2), osteoblasts retract and give place to the osteoclasts, which can adhere to the extracellular matrix. Vitamin D and PTH stimulate osteoclast activity, whereas calcitonin inhibits it. Oncogenes c-fos and c-myc are expressed in osteoblast proliferation[5,6].

Cartilage growth regulation is complex and is under hormone action – growth hormone, IGF1 and 2, estrogens, and androgens, but also a number of locally produced factors (FGF2, TGFb, epidermal growth factor [EGF], platelet-derived growth factor [PDGF])[5].

Estrogens act by hastening chondrocyte proliferation, and the androgen action on cartilage is ensured by the activation of estrogen receptors, as the androgens synthesized by gonads penetrate the chondrocytes, where they are transformed into estrogens by the enzyme aromatase[7,8].