Effect of the physical activity on normal bone and on the osteoporosis prevention and treatment*

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ABSTRACT

Osteoporosis has been increasingly diagnosed in women and men worldwide. Although the sexual steroids are important in the genesis of human osteoporosis, it is believed that the lack of physical activity constitutes a risk factor. Physical activity acts on the bone by direct effect via mechanical force, or indirect effect through hormonal factors. However, the mechanism through which physical activity improves the bone mass is not completely known. Sports practice has been increasingly recommended for prevention and even treatment of osteoporosis based on the results that have demonstrated the beneficial effects of physical activity on the bone tissue. The goal of this review is to describe the effects of physical activity in the normal bone tissue and on the osteoporosis prevention and treatment.

INTRODUCTION

Osteoporosis is an increasingly diagnosed disease in women and men worldwide with the life expectancy (1). Much has been said about the role of the sexual steroids deficiency in the osteoporosis genesis, mainly of menopause, but it is also known that the lack of physical activity is an important risk factor (2).

Although physical activity shows powerful and complex effect over the bone tissue directly or indirectly, research results are contradictory yet and dependent on the frequency, duration and exercise intensity (2). The effect of exercising over some bones, evaluated through densitometry or bone biopsy, is insufficient to provide any conclusion about the whole skeleton response to physical stimulus. Thus, the histological and morphometrical studies of different bones and with distinct metabolisms are essential to a better understanding of the benefits of physical exercise over the whole skeleton, once the bones have differentiated metabolism and can present distinct response to many different stimuli, no matter if nutritional, hormonal or physical.

The aim of this review is to describe the effects of physical activity in the normal bone tissue and in the prevention and treatment of osteoporosis.

THE NORMAL BONE TISSUE

The bone is a multifunctional tissue consisted of three cell types: the osteoblasts, the osteocyte and the osteoclasts. The first cell type derives from the osteoprogenitor cells of the bone marrow and is located on the surface of the trabeculae; in the Havers channel of the osteonic bone tissue and in the periosteum. Its main function is synthesizing the bone matrix and mineralization (3) consisted of collagen type I, of non-collagenic proteins (fibronectin, tenascin and osteopontin), of \( \lambda \)-carboxilated proteins (osteocalcin and Gla protein) and of proteoglycans (condroitin sulphate), among others (4). An average of 70% of the non-mineralized bone marrow matrix is mineralized right after its synthesis and the residues suffer gradual mineralization (5).

As soon as the bone matrix is synthesized, the osteoblasts are involved by it and are called osteocyte. Such cells have the function to keep the bone tissue viability (6) and reabsorb the matrix and the bone minerals through the osteolysis, deep reabsorption mechanism, essential to keep the extracellular calcium levels stable (7). The osteocyte place themselves in columns inside the mineralized bone tissue and communicate with other osteocyte and osteoblasts through interchannel projections, the gap junction (6). Such junctions are intramembranous channels consisted of proteins known as connexins (Cx) and that promote the communication between the cytoplasm of two neighbor cells allowing the passage of metabolites, ions and intracellular signal molecules, such as calcium and AMPc (8).

The osteoclasts are multinuclear cells derived from the fusion of the hematopoietic mononuclear cells with differentiation dependent on factors liberated by the osteoblastic lineage cells.

The osteoclasts are on the surface of the trabeculae and the Havers channels and in the periosteum, placed in the Howship columns. Whenever they are activated, their main function is to promote the bone reabsorption by osteoclasia (9).

The bone is responsive to a series of stimuli due to its multifunctional tissue constitution, among them we can mention biological, biochemical and biomechanical ones.

THE BONE TISSUE AND OSTEOPOROSIS

The bone is a metabolically dynamic tissue and its hardness depends on the balance between the anabolic (aposition) and catabolic (reabsorption) processes. It is known that the genetic constitution, the diet and the physical stimuli are factors that influence the bone metabolism, but the effective bone apposition and reabsorption is mediated by hormones, cell products and by the bone matrix.

The catabolic process or bone reabsorption, has the vital function of keeping stable the extracellular calcium levels. The bone apposition (the bone matrix synthesis and mineralization) has two main objectives that are to re-put the bone tissue lost by the catabolic process and fulfill the organ needs in adapting to the functional conditions. Imbalances between these two processes have been accumulated throughout one’s lifetime, especially due to isocalcemia (10, 11). As a consequence of the supremacy of the catabolic process, we have the bone loss, especially if inhibiting factors of the bone neoformation – as the ones inherent to the senescence are associated. Thus, changes in metabolism, in the calcium absorption and in the hormonal profile – specially in women after menopause – associated to physical inactivity, contribute to an...
imbalance to the bone remodelling, having osteoporosis as the main consequence. Osteoporosis is a generalized metabolic disease, characterized by lower bone apposition due to osteoblastic insufficiency, with bone mass reduction by volume unit and by multifactor etiology. Concerning the sexual hormones deficiency in the menopause osteoporosis genesis, a lot of attention is given, once the sexual hormones production ceases, the feminine bone mass decreases rapidly in the first 10 years and slowly in the following years. Moreover, a smaller quantity of bone is found and a greater quantity of it is reabsorbed in each remodelling cycle. Estrogen and progesterone act in the bone remodelling, however, by mechanisms not totally clear. The presence of receptors to estrogen in osteoblasts and osteocytes suggest a direct effect of this hormone over the bone tissue. Concerning the osteoblasts, estrogen increases these cells differentiation and stimulates the synthesis and the bone matrix mineralization, regulating the expression of genes that encode the type I collagen and the non-collagenic proteins such as osteopontin, osteocalcin, osteonectin, and so forth. Besides that, estrogen indirectly inhibits the bone reabsorption when it regulates the synthesis and citocines, prostaglandines and growing factors liberation. Progesterone also participates in the bone metabolism, especially in the bone matrix synthesis. This hormone stimulates the osteoprogenitor cells proliferation and differentiation and works in the osteoblasts regulating the secretion of growing factors and stimulating the bone apposition and mineralization. Thus, the osteopenia observed in the progesterone deficiency seems to be derived from the bone apposition decrease.

The bone mass reduction derived from the hypogonadism, is also related to the intestinal calcium absorption decrease. Estrogen has a direct action over the intestinal mucous membrane and indirect mediated by vitamin D. Thus, in the estrogen deficiency a decrease in the number of receptors for vitamin D in the intestine and smaller renal conversion of inactive vitamin D in its active manner is expected. Consequently, in the hypogonadism, smaller formation of the linking calcium protein decreasing its intestinal absorption is observed.

The T3 and T4 thyroid hormones control the bone metabolism and the mineral homeostasis of adults and the thyroid-osteooporosis relation has been studied for many years. The thyroid hormones and the sexual hormones control the gene expression in the osteoblasts, increasing the alkaline phosphatase activity and the type I collagen and the non-collagenic proteins production and growing factors similar to insulin, increasing the bone matrix synthesis and mineralization after that. In the thyroid hypofunctions, general metabolism is reduced, which directly affects the recruiting, the differentiation, the maturation and the metabolism of cells responsible for bone apposition, mineralization and reabsorption with osteoporosis as a consequence. In the hypothyroidism, the bone matrix mineralization decrease seems to be due to the calcium and phosphorus plasmatic values decrease, once the thyroid hormones (T3 e T4) are important in the intestinal transportation of calcium and phosphorus mediated by 1,25(OH)2D3.

Hormonal factors are not the only ones involved in the osteoporosis genesis. It is believed that the lack of physical activity is a risk factor, once extensive evidence has been connecting physical activity to bone loss. It was demonstrated in humans a deduction of 0.9%/week of the trabecular bone volume associated to the 1.3%/day decrease of the muscular contraction force after extended immobilization. Physical activity has been adopted as a strategy to prevent mineral bone loss and to keep the skeleton integrity, since there is a close relation between physical activity, mineral bone density and bone mass. However, some mechanisms through which physical activity works in the bone tissue and through which the physical inactivity promotes bone loss, have not been clarified.

PHYICAL ACTIVITY EFFECT OVER THE BONE TISSUE

The majority of researchers agree that physical activity presents powerful and complex effect over the bone. Yet, the research results are still contradictory. No alteration, increase and even bone mass reduction have been described in female rats submitted to physical activity. There is also evidence that in humans, physical exercises developed in the growing and development phases, determine a 7 to 8% of bone mass gain in adults, reducing substantially the breaking risks in advanced age. It is obvious that depending on the kind and exercise intensity, the effects over the bone tissue vary, and can be deleterious. Intense sports activity may lead to osteoporosis, to damage of the gonadotropin hormone pulsing (GnRH) and to gonadal disfunction in young adults and not protect women against bone loss in menopause. Pre-puberty gymnasts submitted to intense exercising present growing delay and higher frequency of locomotory disorders, besides the reduction of the growth factor similar to the insulin-1 (IGF-1) and the thyroid hormones and blood cortisol increase. Similar results were observed in female rats in the growing phase, submitted to moderate impact physical activity (treadmill running). Such animals presented osteoporosis in the nasal bones and chest vertebrae, probably caused by the hypothalamus-hypophysis-ovary axis suppression.

There is evidence that physical activity minimizes the osteopenia derived from age advance and the sexual steroids decline. However, not every kind of exercise promotes benefits over post-menopause women’s skeleton. Some studies demonstrate that moderate load exercises such as walks and cooper, promote increase in the bone minerals of those women. On the other hand, it was observed that in post-menopause women submitted to low load physical exercises, such as swimming, that these are beneficial to the cardiovascular conditioning, but do not promote change in the bone tissue variation. In castrated female rats with osteoporosis daily submitted to controlled and systematic treadmill running, physical exercise promoted not only bone mass gain in the whole skeleton when compared to the bone tissue quantity before the exercise, but also made the bone tissue quantity equal in some sites of the skeleton, or even greater than in the normal groups.

Moreover, it is also proved that physical exercise with moderate load, help in the maintenance or bone mass gain in post-menopause women. In that same phase, physical activity almost always causes anabolic effect when associated to a conventional kind of osteoporosis treatment.

Physical activity promotes changes in the bone metabolism through direct effect, via mechanical force, or indirect, promoted by hormonal factors. The mechanical force when applied over the bone tissue forms endogenous signs that interfere in the processes of bone remodelling. Such signs are captured by a mecanosensoric system in which the osteocyte is the main cell responsible for translating the mechanical force into biochemical signs that regulate the bone turnover. It is believed that the cell deformation caused by direct force over the cell, the intracanalicular pressure increase caused by dynamic force and the increase of the interstitial fluid flow speed, are factors that directly affect the osteocyte, being the last one, the higher stimulus to the osteocyte in response to mechanical load. The interstitial fluid flow through the canalculus around the osteocyte, seems to be responsible for the extracellular matrix deformation and for changes in the cellular membranes. Physical activity also promotes increase in the canalculus branching connections of the osteocytes, increasing the bone matrix viability.

Concerning the effect of the mechanical force over the osteocytes, a lot is speculated about the autocrine function of the E2 prostaglandine (PGE2) in the gap junctions regulation and in the
CX43 expression in the osteocytes membrane. The conversion of the arachidonic acid into E2 prostaglandine is observed in the osteocyte when mechanical force is applied. Its liberation would act as an autocrine factor, once increase in prostaglandine liberated in the bone immediately after a mechanical force imposed by weight lifting, has been described in humans. A PGE2 connects to its receptor expressed in the osteocyte membrane increasing the AMPc concentrations and stimulating the CX43 protein formation and new gap junctions. However, the prostaglandine effect over the skeleton is controversial. It usually acts as an anabolic agent, since that the prostaglandine administration in osteoblasts culture increases the number and activity of those cells, with increase in the bone matrix synthesis as a consequence. Its catabolic effect stimulating the formation and osteoclasts activity has been already described, though. It is believed that the distinct effects of the PGE2 over the bone are due to their many subtypes of receptors, such as EP1, EP2, EP3 and the EP4, connected to the G specific proteins. The exact function of these receptors over the bone cell, especially over the osteocyte, is unknown yet. It has been demonstrated that the EP2 receptor expression increases in response to the interstitial fluid flow. Although it has been already described that the prostaglandine in vivo, activates the bone remodeling, in intact and oophorectomized animals, it is unknown what would be the prostaglandine participation as intermediary of physical activity effects in the skeleton with osteoporosis.

In an evaluation of the physical activity effect in the whole skeleton in the osteoporosis treatment, it was observed that after three months of physical activity, the thickening of the nasal bone of female rats with osteoporosis submitted to daily physical activity, was significantly higher in relation to sedentary animals with osteoporosis and even in relation to normal animals. However, the nasal bone does not suffer any kind of impact during exercising, suggesting that the beneficial effect caused by physical activity is not only mediated by the mechanical force, but also by hormones and growing factors.

The indirect effect of the physical activity over the bone put into action by hormonal factors, comprehends the citocines production and the liberation of growing factors by osteocyte, consequently, with the increase of the osteoblastic activity. Besides that, the physical activity triggers a series of physiological responses involving the hypothalamus-hypophysis-adrenal and hypothalamus-hypophys-gonades. The physical activity stimulates the secretion of the growing hormone (GH) that has direct or indirect anabolic effect, via growing factor similar to the 1 insulin (IGF-1). The IGF-1 is a citocine that stimulates the DNA synthesis and consequently promotes the collagen synthesis by the osteogenic cells, increasing the in vivo bone matrix formation. Studies report that six hours after exercise there is an increase of the RNAm levels of IGF-1. However, the liberation of IGF-1 in the physical activity is controversial. It is claimed that in humans, even without plasmatic increase, the IGF-1 local liberation is the responsible for the exercise anabolic effect over the bone tissue.

The circulant thyroid hormones and the cortisol secretion also increase during physical activity. However, no mention is done about their participation as intermediary of the physical activity effect in the bone metabolism. Similar comment is made about the paratormonoium (PTH), whose concentrations suffer no change or increase during or after physical activity. Differently, the sexual steroids can have their secretion inhibited by physical activity, with delay of sexual maturity and if the activity is conducted with inadequate intensity, may cause hypostrogenism or hypoprogenism.

Physical activity affects the bone not only as tissue, but also as an organ for its action in the growth cartilages. The mechanical stress regulates the cartilage momeostasia not only during the endochondral growth, but also during the fractures repairing. The cartilage growing process basically involves three stages: the first consists of the chondrocytes activation in rest and the type II collagen production and the agrecan by the cells. The second stage is marked by the cease of the cellular proliferation, with the chondrocytes maturation and increase of the cartilage matrix synthesis. The last growing stage is characterized by the chondrocytes hypertrophy and type X collagen synthesis. During this stage yet, the chondrocytes go into apoptosis, the bone matrix is synthesized over the cartilage skeleton which is later removed. The mechanism through which the mechanical force regulates the cartilage growth, changing the chondrocytes proliferation, maturation, hypertrophy and apoptosis has not been totally elucidated yet. It has been reported that the mechanical force promotes matrix deformations in the cartilage, eletrocinetic effects, hydrostatic pressure changes and increase in the interstitial fluid flow. According to these researchers, all these factors would be important in the mechanotransduction process of the mechanical sign. It has also been reported that ionic channels, especially the calcium ones, would be responsible for transmitting the mechanical sign to the cell, stimulating then the chondrocytes proliferation, maturation and hypertrophy. It is also mentioned that, the opening and closing control of these ionic channels would be done by the collagen matrix deformation caused by the mechanical stress.

PHYSICAL ACTIVITY EFFECT OVER THE BONE MARROW

The bone as an organ consists of many mesenchemical cells, among them are the osteoblasts, the chondrocytes, the myoblasts and the marrow stroma cells, including the adipocytes. It is believed that all these cell lineages are originated from progenitor cells called bone marrow stroma-stem-cells (MSCs). The bone tissue is constantly renewing during one’s lifetime and, such process demands the recruiting and proliferation of stem-cells able to differentiate into osteoblasts which will synthetize and mineralize the bone matrix. The MSCs offer osteoprogenitor cells and evidence in literature is found reporting that bone marrow cells transplant in the epiphysis of mice long bones promoted repopulation of cells able to differentiate into functional osteoblasts, which reinforces the importance of the marrow stroma cells in the osteoblastic differentiation.

The main factors that stimulate the marrow cells differentiation into osteoprogenitor cells have been subject to research. Although the factors that stimulate the bone marrow in the supply of osteocyte are not completely reported, it is known that the E2 prostaglandine, the growth hormone, the IGF1 and the bone morphogenetic proteins are important factors to the marrow osteoprogenitor cells recruiting. Besides that, recent studies have shown that bone marrow stroma cell cultures in vitro, submitted to mechanical stimulation present greater differentiation to cells able to produce bone matrix. A similar result in vivo was observed, in which physical activity promoted osteoblastic hyperplasia and increase of the red bone marrow/ yellow bone marrow ratio in the osteopenic skeleton. Physical activity increases the inncannular fluid speed inside the osteocyte and consequently increases the E prostaglandine levels that present autocrine action in the bone, stimulating the marrow stroma cell differentiation in osteoprogenitor cells.

FINAL CONSIDERATIONS

Although some results are contradictory, literature is clear about the beneficial effects of physical activity over the bone tissue in normal individuals and in osteoporosis prevention and treatment as well. Yet, the mechanisms through which the physical activity stimulates the osteoblastic differentiation from bone marrow stroma cells should be better elucidated. Such field is a promising one, especially with the expectation increase concerning the stem-cells for diseases treatment. Once the factors and mechanisms through which physical activity increases the bone mass in osteopenic in-
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