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The roles of exercise in bone remodeling and in prevention and treatment of osteoporosis

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ABSTRACT

With a rapid increase in the aging population, osteoporosis has become a global health problem. Although anti-resorption and anabolic drugs are available, osteoporosis cannot be completely cured. Exercise is an economical, efficacious, and safe way to prevent the development of osteoporosis. Recent studies have investigated the mechanisms by which exercise affects bone remodeling. Here we update the progress made on the effects of exercise on bone cells, including bone marrow mesenchymal stem cells, osteoblasts, osteocytes, and osteoclasts, as well as on bone mass, bone strength, and geometry, hoping to provide a theoretical basis to improve osteoporosis prevention and treatment with exercise.
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1. Introduction

With an increase of aging population, the morbidity rate of osteoporosis is continuing to escalate, which has now become a major public health problem in the world (Harvey et al., 2014). Osteoporosis is a metabolic bone disease with systemic osteopenia, bone microstructure deterioration, increased osteopsathyrosis, and decreased bone strength (Cummings and Melton, 2002). The patients with osteoporosis may suffer from whole body pain, decreased body height, kyphosis, fractures, and other clinical symptoms, which compromise the quality of life of the patients. Drug therapy is the main way to treat osteoporosis, yet osteoporosis cannot be completely cured with the available drugs. In addition, some of the drugs have side effects such as increasing the morbidity rate of reproductive system cancer, esophageal cancer, and cardiovascular diseases (McClung et al., 2013).

Osteoporosis is caused by disruption of the balance between bone formation and resorption (Chen et al., 2014; Li et al., 2015a,b, 2009). Bone formation is carried out by osteoblasts and resorption is carried out by osteoclasts(Cheng et al., 2013; Yang et al., 2012). Osteoblasts are derived from mesenchymal stem cells (MSCs) through several stages including osteoprogenitors and preosteoblasts, whereas osteoclasts are derived from the macrophage lineage of hematopoietic stem cells (HSCs). In response to bone stimulating signals, MSCs can differentiate into osteoblasts and then osteocytes (Thompson et al., 2012). During the progressive stages of the osteoblast differentiation, the level of alkaline phosphatase (ALP), osteocalcin (OCL), Runx2, osterix (Osx) are increased and they are considered as osteogenic markers (Chen et al., 2004; Hu et al., 2011). Osteoblasts also express osteoprotegerin (OPG) and receptor activator of nuclear factor κB ligand (RANKL) and macrophage colony-stimulating factor (M-CSF) to regulate monocyte-to-osteoclast differentiation (Kreja et al., 2008).

It is well known that the bone is responsive to mechanical loading, which acts on the bones through both muscle forces and ground reaction forces (Yokota et al., 2011). These forces increase both bone mineral density and strength, which may be one of the main reasons why exercise can improve bone health. Owing to its pro-osteogenic effects and the lack of adverse side effect (Cheung and Giangregorio, 2012; Niinimaki, 2012), exercise has been widely recommended to prevent osteoporosis. Exercise performed

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during the growth phases has been shown to increase the peak bone mass, which reduces bone fracture risks in advanced age (Burrows, 2007). Yet, the exact mechanisms whereby exercise affects bone remodeling remain unclear. The aim of the review is to update our understanding of the roles of exercise played in bone remodeling and in prevention and treatment of osteoporosis, with an emphasis on bone cells, bone mass, bone strength and geometry, and the molecular mechanisms by which exercise executes these effects.

2. Effect of exercise on bone cells

2.1. Bone marrow mesenchymal stem cells

Bone marrow mesenchymal stem cells (MSCs) are multipotent cells that have the capacity to proliferate and differentiate into various mesenchymal cell lineages including osteoblasts, chondrocytes, and adipocytes. Exercise has been shown to induce MSCs to differentiate towards osteoblasts. A recent study compared the effects of endurance training and sedentary lifestyle on MSCs in four-week-old male C57Bl/6 mice and found that endurance training could increase the total number of bone marrow MSCs, enhance the osteogenic differentiation potential of MSCs, and inhibit the adipogenic potential of MSCs (Maredziak et al., 2015). Enhanced osteogenic differentiation is manifested by an increase in the activities of ALP and the levels of osteopontin (OPN) and OCL, the osteoblast markers. Another study also reported that physical activity could increase the number of mineralized nodules, and the expression of OCL and ALP in the MSCs of adult rats (Hell et al., 2012). Similarly, physical activity increased osteogenic differentiation of ex vivo cultured MSCs that were isolated from osteopenic adult female rats. This beneficial effect of exercise was mediated by increased production of nitric oxide (NO), which was shown to have strong stimulatory effect on osteogenic differentiation of MSCs (Ocarino et al., 2008).

2.1.1. The signaling pathways

Bone formation begins with stem cell proliferation and condensation. The condensed mesenchymal stem cells differentiate directly into osteoblasts during intramembranous ossification, whereas they differentiate into chondrocytes and form the initial cartilage templates during endochondral ossification. Two transcription factors, Sox9 and Runx2, play essential roles in the differentiation of MSCs. Sox9 directs early chondrogenic differentiation and cartilage formation while Runx2 directs osteoblast differentiation and bone development.

The TGF-β and BMP family have been shown to regulate osteoblast differentiation and bone formation (Chen et al., 2012). TGF-β was shown to promote osteoprogenitor proliferation and commitment and early differentiation of the osteoblastic lineage through activating selective MAPKs and the Smad2/3 pathway, both of which play a crucial role in Runx2 expression in response to TGF-β (Lee et al., 2002). BMPs, as a subfamily of the TGF-β superfamily, also play pivotal roles in osteoblast differentiation. BMPs induce the expression of Runx2 and the p38-mediated phosphorylation of Runx2, thus promoting MSC osteogenic differentiation (Phimphilai et al., 2006). In particular, BMP-2, BMP-4, and BMP-7 have been extensively studied in MSC osteogenic differentiation and bone formation. Short-term BMP-2 expression is sufficient to induce osteochondral differentiation of MSCs in vivo (Noel et al., 2004). BMP-7 was able to up-regulate the expression of ALP and accelerate calcium mineralization in human bone marrow MSC cultures (Shen et al., 2010).

There is evidence that exercise can regulate bone metabolism and MSC osteogenic differentiation through the BMP signaling pathways. It was reported that the BMP-2 mRNA levels were increased in bone marrow cells after climbing exercise (Menuki et al., 2008). Swimming was also shown to increase the mRNA levels of BMP-6 during the initial stages of MSC chondrocyte differentiation in female rats (Yamada et al., 2002).

It has been widely recognized that the canonical pathway of Wnts, the β-Catenin signaling pathway, is critical in regulating osteoblast and chondrocyte differentiation from mesenchymal progenitors (Day and Yang, 2008). Mutations in this pathway have been shown to result in low bone mass (Gong et al., 2001). The Wnt-β-Catenin signaling can promote Runx2 expression and this prevents chondrocyte differentiation by inhibiting Sox9 expression during intramembranous ossification. During endochondral ossification, the Wnt-β-Catenin pathway is inhibited, leading to an increase in Sox9 expression and a decrease in Runx2 expression. However, the Wnt-β-Catenin pathway is activated to upregulate Runx2 expression in the perichondrium during the later stages of endochondral ossification, which leads to the formation of the bone collar (Day et al., 2005).

Exercise can induce mechanical stress on the bone (Cheung and Giangregorio, 2012; Niinimaki, 2012). Exercise might regulate osteoblastic differentiation of mesenchymal precursors through mechanical loading-activated Wnt signaling. Eight weeks of power training could significantly upregulate the levels of Wnt1 mRNA and the levels of β-Catenin protein in physically active young men (Leal et al., 2011). Treadmill training was shown to increase the protein levels of β-Catenin and inhibit the production of PPARγ in lumbar vertebrae of ovariectomized (OVX) rats, demonstrating exercise's positive role in the prevention of bone loss in OVX rats (Bu et al., 2012). A recent study has shown that resistance exercise could increase the level of Wnt4 and β-Catenin in young men (Spillane et al., 2015). The levels of Runx2, the key effector molecules of the Wnt signaling pathway in MSCs, were shown to gradually increase under strain stimulation (Li et al., 2015a,b). It was also reported that resistance exercise could upregulate the expression of Runx2 in rats (Notomi et al., 2014). These findings suggest that exercise may execute its positive effects on the bone and MSC osteogenic differentiation by up-regulating the expression of Wnt molecules.

2.1.2. Mechanical loading

Accumulating evidence suggests that mechanical stimuli affect MSCs, osteoprogenitors, osteoblasts, and the terminally differentiated osteocyte (Thompson et al., 2012). It has been shown that mechanical loading has a positive effect on osteogenic differentiation of MSCs. Moreover, there is a strong evidence that unloading leads to rapid loss of bone in the affected limb, which is associated with an enhanced adipogenic differentiation of the bone marrow MSCs (Meyers et al., 2005).

Exercise in general leads to an increase in mechanical signals such as fluid flow, dynamic tension, compression, and hydrostatic pressure. These mechanical signals promote MSCs osteogenic differentiation and inhibit adipogenic differentiation, which may be one of the main reasons why exercise prevents the development of osteoporosis. It is worth mentioning that mechanical signals can control MSC lineage fates through β-Catenin, in a LRP5 or LRP5 receptor-independent manner though LPR5/LPR5R is considered as a mechanoreceptor in bone cells (Sawakami et al., 2006). Fluid flow can regulate osteogenic differentiation of MSCs as well. Fluid flow up-regulates the expression of Runx2 and Sox9 in murine C3H10T1/2 (a MSC line) through the Wnt5a-β-Catenin pathway and the non-canonical Wnt signaling pathways (Arnsdorf et al., 2009).

Tensile strain, another kind of mechanical force, also plays an important role in MSC osteogenic differentiation. The study of 3D cultures (in collagen matrices) of bone marrow-derived hMSCs

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