

Review

Exercise as an Adjuvant to Bone and Cartilage Regeneration Therapy

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Abstract:

This article provides a brief review of the ontogeny of chondrocytes and the pathophysiology of osteoarthritis (OA), and details how physical exercise improves the health of osteoarthritic joints and enhances the potential of mesenchymal stem cells for successful transplantation therapy. In response to exercise chondrocytes increase their production of glycosaminoglycans, bone morphogenic proteins and antiinflammatory cytokines and decrease their production of proinflammatory cytokines and matrix degrading metalloproteinases. These changes are associated with improvements in cartilage organization and reductions in cartilage degeneration. Studies in humans indicate that exercise increases peripheral blood recruitment of bone marrow-derived mesenchymal stem cells (BM-MSC) and upregulates BM-MSC expression of osteogenic and chondrogenic genes, osteogenic micro-RNAs, and osteogenic growth factors. Rodent experiments are uniform in demonstrating that exercise enhances the osteogenic potential of BM-MSC while diminishing their adipogenic potential, and that exercise done after stem cell implantation may benefit stem cell transplant viability. Physical exercise also exerts a beneficial effect on the skeletal system by decreasing immune cell production of osteoclastogenic cytokines interleukin (IL)-1 β , tumor necrosis factor (TNF)- α , and interferon (INF)- γ while increasing their production anti-osteoclastogenic cytokines IL-10 and transforming growth factor (TGF)- β . In conclusion, physical exercise done both by stem cell donors and recipients may improve the outcome of mesenchymal stem cell transplantation.

Keywords Exercise; osteoarthritis; osteoporosis; mesenchymal stem cells; hematopoietic stem cells; stem cell transplantation; chondroblasts; chondrocytes; cytokines.

1. Introduction

In the global burden of disease 2010 study, osteoarthritis accounted for 17,135 years of life lived with disability (YLD), an increase of 64% when compared to YLD of 1990. Overall, musculoskeletal disorders (which included inflammatory causes of arthritis) accounted for 6.8% of total YLDs [1] with osteoarthritis ranked as the 11th leading cause of disability worldwide [2]. In addition, an estimated nine million osteoporotic fractures occurred globally in the year 2000 resulting in a loss of 5.8 million Disability Adjusted Life Years and accounting for 0.83% of the global burden of noncommunicable disease [3]. In 2011, 1.7 million people were hospitalized in the United States for osteoporosis-related fragility fractures at a cost of over 70 billion dollars [4]. In 2015, the prevalence of osteoporotic vertebral fractures in caucasian women ≥ 50 years of age from North America was estimated at 20-24%; in Europe, the prevalence varied between 18% and 26% [5]. Overall, osteoporosis is estimated to occur in one in three women and one in 12 men [6]. And the global prevalence of osteoarthritis and osteoporosis is expected to increase as the average age and weight of the World's population increases.

Physical exercise has long been recognized as an essential factor in the maintenance of bone health, particularly during adolescence when $\sim 50\%$ of bone mass accretion occurs [4]. The 2019 American College of Rheumatology/Arthritis Foundation guidelines for the management of osteoarthritis of the hip and knee emphasized the importance of regularly performed physical exercise [7]. Both traditional (resistance, aerobic and flexibility) and non-traditional (Tai Chi, yoga, aquatic) exercises have been shown to be effective in the management of knee and hip osteoarthritis [8]. In addition, clinical trials have shown that multicomponent training (aerobic and resistance exercises) is effective in increasing bone mass in osteoporotic women [9]. In this regard The World Health Organization recommends that adult men and women should accumulate at

least 150 min of moderate intensity physical activity per week and young people aged 5–17 years should accumulate at least 60 min of physical activity of moderate to vigorous intensity daily [10].

There is increasing interest in treating bone and cartilage disease with mesenchymal stem cell (MSC) implants [11-17]. Bone marrow-derived MSC, adipose tissue derived MSC, and umbilical cord-derived MSC been shown to have beneficial effects in osteoporotic animals, and intravenous administration of autologous fucosylated bone-marrow-derived MSC to patients with osteoporosis is currently in a phase I clinical trial. MSC transplants have the potential to repair bone by differentiating into osteoblasts and chondrocytes and by secreting growth factors that stimulate osteoblastogenesis and angiogenesis and inhibit osteoclastogenesis [18].

In this article I review the pathophysiology of osteoarthritis (OA) and detail how physical exercise improves the health of articular cartilage and chondrocytes in OA and enhances the potential of mesenchymal stem cells for successful transplantation therapy. I also discuss how exercise protects the skeletal system by upregulating the production of antiosteoclastogenic cytokines and downregulating the production of osteoclastogenic cytokines by chondrocytes and peripheral blood mononuclear cells

2. Materials and Methods

This narrative review is on exercise as an adjuvant to bone and cartilage regeneration therapy. The research strategy included the following: 1. defining the key topics; 2. identifying key words or synonyms that represent each of the key topics; 3. an online PubMed search of key topics and key words; and 4. a refinement of the search based on initial findings. Data restrictions included articles with identical samples and identical outcomes, identical samples with different outcomes, increased samples and identical outcomes, and decreased samples with identical outcomes. Key

topics included exercise and osteoarthritis, exercise and osteoporosis, exercise and bone remodeling, exercise and bone homeostasis, exercise and mesenchymal stem cells, exercise and mesenchymal stromal cells, exercise and hematopoietic stem cells, exercise and osteoblasts, exercise and osteocytes, exercise and osteoclasts, exercise and osteogenic hormones, exercise and pro-inflammatory cytokines, exercise and anti-inflammatory cytokines, exercise and myokines, stem cell therapy of osteoarthritis, and stem cell therapy of osteoporosis. Keywords included exercise, osteoarthritis, osteoporosis, osteoimmunology, osteocytes, osteoblasts, osteoclasts, mesenchymal stem cells, hematopoietic stem cells, cytokines, interleukins, macrophage colony stimulating factor, receptor activator of NF κ B ligand, receptor activator of NF κ B, osteoprotegerin, tumor necrosis factor- α , and sclerostin.

3. Pathophysiology of osteoarthritis

In addition to tissue fluid, which comprises about 65-85% of its mass, articular cartilage is comprised of type II collagen and proteoglycans (15-22% and 4-7% by weight, respectively). Proteoglycans include the small leucine rich decorin, lumican, biglycan, fibromodulin, lumican and epiphygan, and the heparin sulfate proteoglycan perlecan. Other collagens (types V, VI, IX, X, XI, XII, IV), cell adhesins, growth factors, and cytokines are also present. The predominant cell in articular cartilage is the chondrocyte, which is responsible for maintaining articular homeostasis by replacing degraded matrix with newly synthesized components [19]. Also present in articular cartilage, synovium and synovial fluid are mesenchymal stem cells, which may serve as a valuable source of stem cell transplantation in the treatment of OA [20].

Osteoarthritis is characterized by early alterations in the organization and molecular composition of the articular cartilage extracellular matrix. This change is met with a compensatory proliferative response of chondrocytes and an increase in chondrocyte matrix synthesis. With time,

chondrocytes become senescent, a phenotype associated with the secretion of proinflammatory cytokines and matrix degrading proteases and a reduction in the secretion of antiinflammatory cytokines [21-23]. Senescent chondrocytes eventually undergo apoptosis terminating articular cartilage synthesis [21]. Other metabolic derangements involving transforming growth factor (TGF)- β , fibroblast growth factor (FGF)-2, FGF-18, growth differentiation factor (GDF)-5, and hypoxia-induced factor (HIF)-2a may also contribute to the pathogenesis of osteoarthritis [19].

Studies on menisci, which contain multiple subpopulations of cells responsible for tissue repair and maintenance (“fibrochondrocytes”) have shown that their production of interleukin (IL)-1 is elevated in OA (109-288 pg/mL). IL-1 is a potent proinflammatory and osteoclastogenic cytokine whose effects on menisci and articular cartilage are catabolic [24].

Studies in mice indicate that nuclear factor of activated T cells 1 (NFAT1), a member of NFAT transcription factors, plays a critical role in maintaining the anabolic functions of adult articular chondrocytes by regulating their expression of matrix degrading proteinases and proinflammatory cytokines. Deletion of NFAT1 in adult mice results in a loss of type-II collagen and aggrecan and an over-expression of matrix degrading proteases and proinflammatory cytokines; this is followed by chondrocyte proliferation and hypertrophy, destruction of articular surfaces, osteophyte formation, and exposure of subchondral bone – findings characteristic of OA [25]. Rodova and associates determined that NFAT1 expression in articular cartilage is regulated epigenetically by histone methylation [26]. The anabolic activity of chondrocytes is maintained by their secretion of growth factors TGF- β , insulin-like growth factor (IGF)-1, FGF-2, FGF-18, GDF-5, and bone morphogenic proteins (BMPs) (Figure 1).

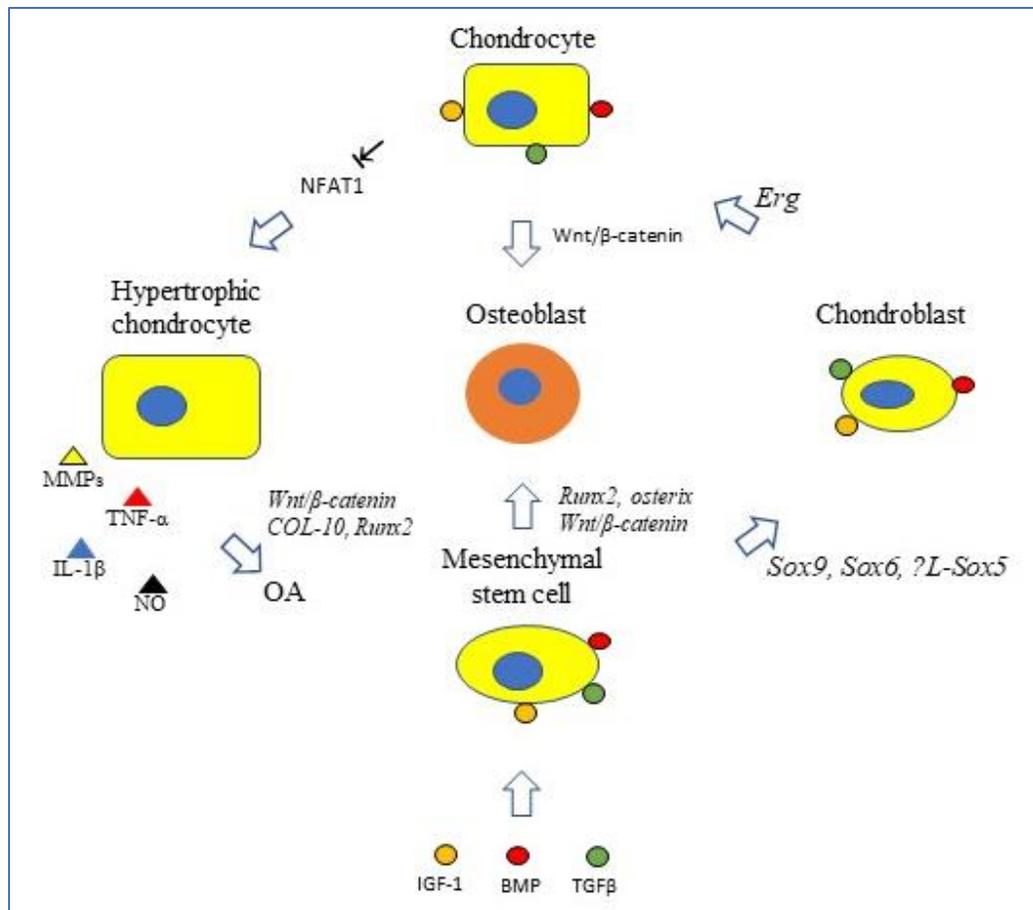


Figure 1. With the aid of growth factors IGF-1, TGF-β, and BMPs, bone marrow mesenchymal stem cells (BM-MSC) expressing *Sox9* and/or *Sox6* differentiate into chondroblasts. Ets-related gene (*Erg*) transcriptional activation prompts chondroblasts to differentiation into mature chondrocytes expressing the transcription factor NFAT1 which plays a critical role in maintaining chondrocyte homeostasis. In adult mice, deletion of chondrocyte NFAT1 results in a loss of type-II collagen and aggrecan and an over-expression of cartilage degrading proteases, proinflammatory cytokines, and nitric oxide (NO); this is accompanied by chondrocyte proliferation and hypertrophy, destruction of articular surfaces, osteophyte formation, and exposure of subchondral bone – findings characteristic of OA.

Wnt/ β -catenin signaling in chondrocytes can prompt their differentiation into osteoblasts, and activation of *runx2* and *osterix* in BM-MSCs prompts their differentiation into osteoblasts. Other growth factors involved in chondrocyte homeostasis are FGF-2, FGF-18, and GDF-5 (not shown).

4. Exercise and osteoarthritis

Although regularly performed moderate intensity exercise is recognized as the mainstay treatment of OA [7,8] there are a limited number of studies sampling constituents of the OA joint before and after supervised exercise training of men and women. One of these was published by Roos and Dahlberg and involved 45 subjects who had undergone medial meniscus resection 3-5 years prior to the study and were at risk of developing OA. Subjects underwent supervised exercise training 3 times weekly for 4 months or were assigned to a noninterventional group. All subjects had the content of their knee cartilage glycosaminoglycan content assessed by delayed gadolinium-enhanced magnetic resonance imaging. Exercise increased cartilage levels of glycosaminoglycan in proportion to the level of physical activity [27].

In a similar study, Munukka and associates assessed the effects of 12 months of leisure time physical activity on the glycosaminoglycan content of femoral cartilages in 76 post-menopausal women with knee OA using delayed gadolinium-enhanced magnetic resonance imaging. They also found that exercise increased the amount of cartilage glycosaminoglycan [28].

Iijima and associates studied the effects of 2-4 weeks of treadmill walking in 24 male Wistar rats with induced damage to their knee joints using micro-computed tomography, histology and immunohistochemistry analysis. They found that exercise prevented the progression of post-traumatic bone and cartilage lesions and increased BMP-2 and BMP-6 expression in the joint superficial zone chondrocytes [29].

Assis and associates studied the effects of aerobic exercise training on an experimental model of knee osteoarthritis in 50 male Wistar rats. Twenty of the rats were trained on treadmills 3 days/week at 16 meters/minute for 50 minutes/day for 8 weeks. The exercising and control rats were sacrificed, and their knee joints assessed by histologic, morphometric and immunohistochemical analysis. Compared to the controls, exercising animals had a better pattern of cartilage organization and less cartilage degeneration. Exercising animals also had lower chondrocyte nuclear or nucleolar expression of IL-1 β , caspase-3 and matrix metalloproteinase (MMP)-13, confirming the ability of aerobic exercise to downregulate proinflammatory and proteolytic pathways in this model of OA [30].

5. Exercise and mesenchymal stem cells

The author is using the International Society for Cell and Gene Therapy committee's recommendation that the acronym "MSC" be used for both mesenchymal stem cells and mesenchymal stromal cells and that the MSC acronym be preceded by "BM" for bone marrow origin and "AD" for adipose tissue origin [31].

5.1. Studies in rodents

Using cultures of BM-MSC flushed from the femurs and tibia of Sprague-Dawley rats, Runguang et. al. found that mechanical strain exerted on the cultures by a FLEXcell-500 device promoted increased BM-MSC expression of osteogenic markers *Runx2*, osterix (*Osx*) and type I-collagen, and decreased their expression of adipogenesis markers peroxisome proliferator-activated receptor- γ (*PPAR γ -2*) and CCAAT enhancer-binding protein α (*C/EBP α*). *Runx2* is the main regulatory gene controlling skeletal development and morphogenesis in vertebrates, *Osx* is a transcription factor for osteoblasts, *PPAR γ -2* is a transcription factor that regulates

differentiation of MSCs into adipocytes, and C/EBP α induces spleen focus-forming virus proviral integrin 1 (PU.1) and interacts with activator protein-1 (AP-1) and nuclear factor kappa-B (NF κ B) to regulate myeloid development. The authors concluded that mechanical strain promotes BM-MSc differentiation into osteoblasts while impeding their differentiation into adipocytes [32]. Liu et. al. reported similar findings in their study on the effects of 8 weeks of treadmill exercise (60 minutes per day at 19.3 meters/minute, 5 degree incline) on the proliferative, differential and apoptotic abilities of cultured femoral BM-MSc. They found that exercise enhanced their osteogenic potential and decreased their adipogenic potential and posited that “BMSc derived from exercised rats on early passage may be a good cell source for bone tissue engineering” [33]. Emmons et. al. report that 15 and 60 minutes of treadmill exercise done by C57 BI/6 mice increased the proliferative capacity of their bone marrow hematopoietic stem cells (BM-HSC) and multipotential HSC progenitors by 40-61%. They attribute these findings to a change in the BM-HSC secretome which included an upregulation of granulocyte-colony stimulating factor (G-CSF) and stem cell factor (SCF) [34]. Bourzac et. al. reviewed literature reports on the effects of physical exercise on MSC proliferation, differentiation and homing and found that the effects of exercise varied depending on the exercise protocol and the tissue from which MSC were obtained; they concluded that “the combination of physical exercise and MSC engraftment improves neural, cartilage, and muscular tissue recovery, but it is not clear whether the effects of MSCs and exercise are additive or synergistic” [35]. Ocarino et. al. studied the effects of exercise on BM-MSc in osteopenic female Wistar rats with and without nitric oxidase inhibition. BM-MSc were isolated from their femurs and cultured in osteogenic medium for 7, 14 and 21 days, phenotyped and analyzed for alkaline phosphatase, collagen synthesis and formation of mineralized nodules. They found that exercise increased BM-MSc osteogenesis

and that inhibition of nitric oxide diminished their osteogenic response. They concluded that “nitric oxide mediates the beneficial effects of physical activity upon MSCs osteogenic differentiation” [36]. Hell and associates measured the effects of exercise on the osteogenic potential of BM-MSC in young and adult female Wistar rats by measuring cell viability, percentage of cells per field, mineralized nodular number and gene expression for telomerase reverse transcriptase (TERT), alkaline phosphatase (AP), caspase 3, osteocalcin, collagen I and sialoprotein. They found that exercise increased the differentiation of BM-MSCs in both study groups, but the effect was greater in young animals than in adults [37]. Using mice, Wallace and associates measured the effects of 5 days of treadmill exercise (30 minutes/day) on BM-MSC and found that exercise increased their osteogenic potential [38]. Yamaguchi measure the effects of exercise on the ability of BM-MSC obtained from male Wistar rats to repair experimentally induced femoral groove osteochondral defects in female Wistar rats. Two weeks after BM-MSC were injected into the defective joints, rats were either sedentary or subjected to 2, 4, or 8 weeks of treadmill exercises performed 5 days/week at 12 meters/minute for 30 minutes; the animals were then sacrificed, and their joints subjected to immuno-histochemical staining. Compared to the sedentary group, they found that exercise enhanced cartilage repair and concluded that their study “highlights the importance of exercise following cell transplantation therapy” [39].

In summary, rodent experiments are uniform in demonstrating that exercise enhances the osteogenic potential of BM-MSC while diminishing their adipogenic potential (Figure 3). In addition, physical exercise done after stem cell implants may benefit stem cell viability.

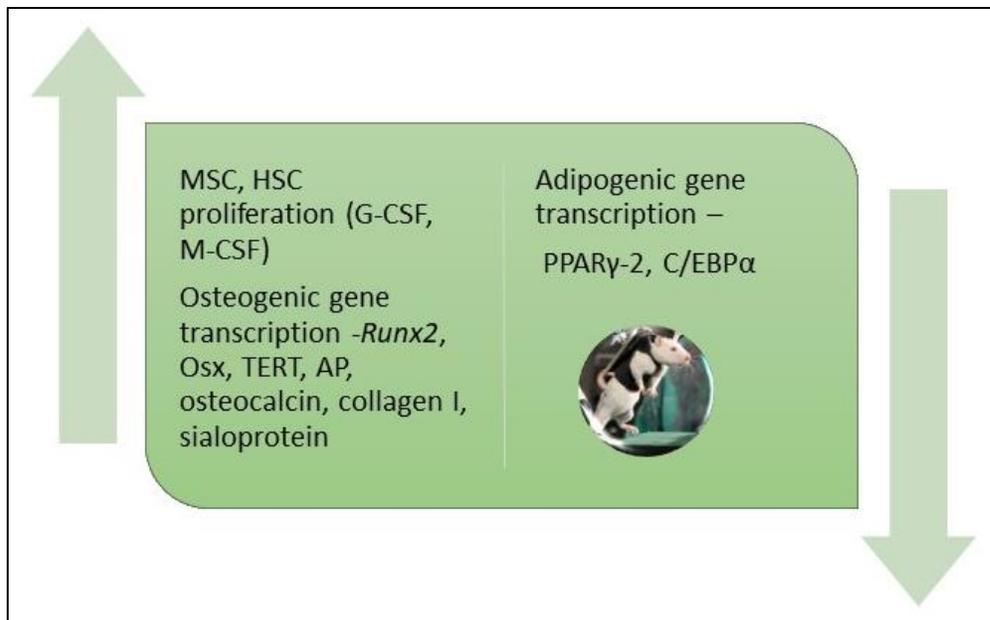


Figure 2. Studies in rodents indicate that exercise increases the proliferation of BM-MSc and BM-HSC and the expression of osteogenic genes, transcription factors, and products while decreasing the expression of adipogenic genes in BM-MSc. G-CSF, granulocyte colony stimulating factor; CSF, colony stimulating factor; *Runx2*, runt-related transcription factor 2; *Osx*, osterix; TERT, telomerase reverse transcriptase; AP, alkaline phosphatase; PPAR γ -2, peroxisome proliferator-activated receptor- γ ; C/EBP α , CCAAT enhancer-binding protein- α .

5.2. Studies in humans

There are a limited number of studies on the effect of exercise on human BM-MSc. Schmidt and associates studied the effects of short term high intensity exercise on the ability of post-exercise sera to influence the proliferation, migration and apoptosis activity of cultured BM-MSc. They found that post-exercise sera enhanced the migratory capacity of BM-MSc, a finding they attributed to the generation of IL-6 by contracting skeletal muscles. They posited that “there is a direct relationship between exercise, IL-6 release and stem cell recruitment” [40]. Carbonare et. al. studied the effects of running one-half a marathon on the differentiation

potential of mesenchymal circulating progenitor cells (M-CPCs) and on the effects of sera on a human bone marrow-derived mesenchymal stem cell line (hBM-MSC) in 22 athletes. They found that exercise upregulated the expression of osteogenic genes *Runx2*, *muscle segment homobox gene 1 (MSX1)*, *secreted phosphoprotein 1 (SPP-1)* and chondrogenic genes *SRY-Box 9 (SOX9)*, *collagen type II alpha-1 gene (COL2A1)*, and apoptosis-related genes *autophagy-related gene 3 (ATG3)* and *Unc-like kinase gene (Ulk1)* in M-CPCs. Also upregulated were BMP 2 and 6. The authors concluded that exercise upregulated the differentiation and apoptosis of BM-MSC [41]. In a study involving 20 amateur runners, Valenti et. al. assessed the effects of running one-half a marathon on the expression of micro-RNAs (miRNAs) in human BM-MSC incubated with pre- and post-exercise sera. They found that exercise upregulated the expression of miRNAs promoting osteoblast differentiation, including miR-21-5p, miR-129-5p, miR-378-5p, and miR-188-p, while downregulating the expression of a miRNA that promotes adipocyte differentiation (miRNA-188-5p). They also found that exercise upregulated the expression of the osteogenic gene *Runx2* [42]. Niemiro et. al. studied the kinetics of progenitor cell mobilization during 60 minute treadmill exercises (70% $V_{O_{2peak}}$) performed by seven men. They found that exercise increased circulating levels of cysteine x cysteine (CXC) chemokine ligand (CXCL)-12 and SCF in hematopoietic stem cells but not in BM-MSC. They concluded that exercise may serve as a valuable adjunct in the context of HSC transplants [43]. Zhang et. al. found that dynamic compression of the type that occurs with exercise increased the expression of chondrogenic genes in cultures of human BM-MSC [44]. Sumanasinghe and associates seeded human BM- MSC in 3D type I collagen matrices and subjected them to 0%, 10%, or 12% uniaxial cyclic tensile strain at 1 Hz for 4 hours/day for 7 or 14 days. They found that BMP-2 mRNA expression and BMP-2 production was upregulated in the strain samples as compared to controls indication

that mechanical strain of the type associated with exercise can induce osteogenic differentiation of human BM-MSC [45].

In summary, experiments in humans, while limited in number, have shown that exercise upregulates MSC and HSC recruitment, enhances osteogenic, chondrogenic and apoptotic gene expression, and upregulates the expression of osteogenic miRNAs and the secretion of growth factors (Figure 3, Table 1).

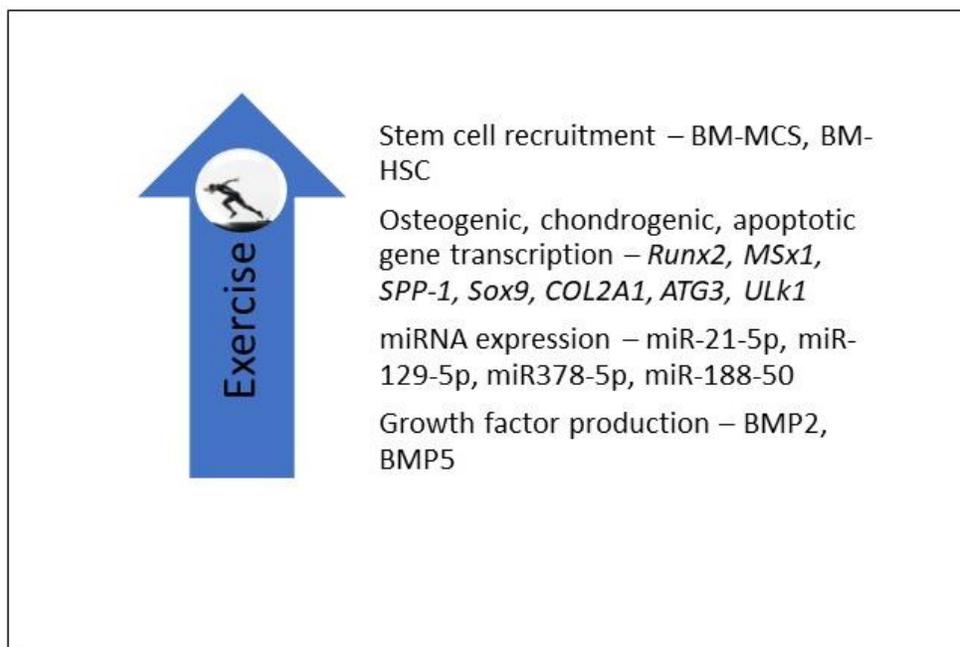


Figure 3. Studies in humans indicate that exercise increases the recruitment of BM-MSC and BM-HSC, and upregulates the expression of osteogenic, chondrogenic, apoptotic genes, osteogenic micro-RNAs, and osteogenic growth factors in BM-MSC. *ATG3*, *autophagy-related gene 3*; *COL2A1*, *collagen type II alpha-1 gene*; *MSx1*, *muscle segment homobox gene 1*; *Runx2*, *runt-related transcription factor 2*; *SPP-1*, *secreted phosphoprotein 1*; *SOX-9*, *SRY-Box 9*; *Ulk1*, *Ul kinase gene 1*; miR, micro-RNA; BMP, bone morphogenic protein.

Table 1. Effect of exercise on mesenchymal stem cells

	Pathways	Genes/transcription factors	mRNAs/miRNAs	Gene products
Osteogenic	↑Wnt/β catenin*	↑ Runx2, osx, MSx1 SPP-1, Sox9, COL2A1, ATG3, Ulk1	↑ ALP, BMP2, BMP4 OCL, I collagen ↑miR-21-5p, miR-129-5p, miR-378-5p	TERT, ALP, caspase3, osteocalcin, BMP2, BMP6
Adipogenic		↓ PPARγ-2, C/EBPα	↓ miR-188-5p	

* The Wnt/β catenin pathway regulates the proliferation, fate specification and differentiation of MSC osteoblast precursors.

6.0. Exercise and osteoclastogenic and antiosteoclastogenic cytokines.

In a before and after trial involving 43 healthy adults Smith and associates measured the effect of six months of combined aerobic, resistance, and flexibility exercises on the production of osteoclastogenic cytokines (IL-1α, TNF-α), anti-osteoclastogenic cytokines (TGF-β, IL-4, IL-10), and cytokines with variable effects on osteoclastogenesis (interferon (IFN)-γ, IL-6) by cultured mitogen-stimulated peripheral blood mononuclear cells (PBMC). Also measured were serum markers of bone formation (osteocalcin) and bone resorption (C-terminal telopeptides of Type I collagen). Exercises done on an average of 2.5 hours a week attenuated the production of osteoclastogenic cytokines and enhanced the production of antiosteoclastogenic cytokines (Figure 2). These changes were accompanied by a 16% reduction in collagen degradation products and a 9.8% increase in osteocalcin levels. They concluded that “Long-term moderate intensity exercise exerts a favorable effect on bone resorption by changing the balance between blood mononuclear cells producing osteoclastogenic cytokines and those producing antiosteoclastogenic cytokines” [46].

Other studies have shown that moderate intensity exercise performed on a regular basis decreases blood levels of osteoclastogenic cytokines and increases blood levels of antiosteoclastogenic cytokines. Santos et. al. reported that exercise training of 22 elderly men for 60 minutes/day, 3 days per week for 24 weeks reduced blood levels of IL-6 and TNF- α and increased blood levels of IL-10 [47]. In a similar study involving 6 months of aerobic or resistance exercise in 80 elderly men, El-Kader et. al. reported that aerobic exercise was superior to resistance exercise in reducing blood levels of IL-6 and TNF- α and increasing blood levels of IL-10 [48,49]. Similar results were reported by Yuan and associates, including exercise-related reductions in osteoclastogenic cytokines IL-1, IL-6, and TNF- α and exercise-related increases in antiosteoclastogenic cytokines IL-2, IL-10, IL-12, IL-13, IL-18, and IFN- γ [50]. In a study involving the effect of acute resistance knee exercise (25 sets of 10 repetitions at 60% of one repetition maximum) in 12 women with knee OA, Helmark et. al. found that exercise increased intraarticular and perisynovial levels of the antiinflammatory cytokine IL-10 as compared to levels found in 13 non-exercising controls [51].

In summary, exercise upregulates PBMC production and serum levels of antiosteoclastogenic cytokines and downregulates PBMC production and serum levels of osteoclastogenic cytokines. In one study, exercise increased intraarticular and perisynovial levels of IL-10 in patients with knee OA (Figure 4).

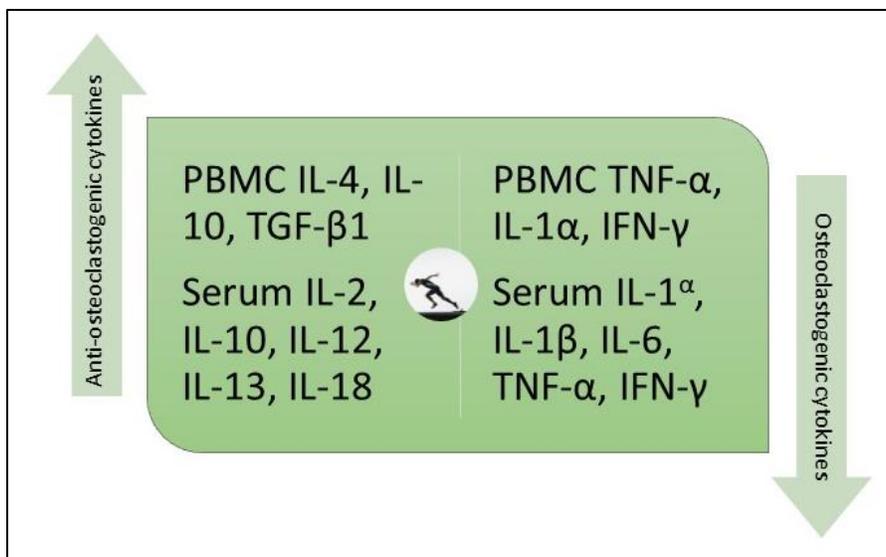


Figure 4. Exercise increases PBMC secretion and serum levels of antiosteoclastogenic cytokines while reducing PMC secretion and serum levels of osteoclastogenic cytokines. PBMC, peripheral blood mononuclear cells; IL, interleukin; TGF-β, transforming growth factor-β; TNF-α, tumor necrosis factor-α; IFN-γ, interferon-γ. *IFN-γ is a pleiotropic cytokines with both antiosteoclastogenic and osteoclastogenic activities which are context dependent.

7.0 Discussion

Mesenchymal stem cells are fibroblast-like cells that arise from embryonic mesenchyme and serve as the source of bone, cartilage, tendon, and adipose tissue. In addition to bone marrow and peripheral blood, MSC are found in the vascular niches of adipose tissue, skeletal and cardiac muscle, lung, cartilage, and tendons. These progenitor cells synthesize and secrete a number of growth factors, extracellular matrix proteins and cytokines that support the growth and survival of hematopoietic stem cells. They are identified by their expression of cell surface markers CD73, CD90, and CD105 and the absence of hematopoietic markers CD14 and CD45. Other criteria include evidence of clonal expansion and/or the capacity to differentiate into multiple

cell types including tendon, cartilage, bone and adipose tissue. MSC represent a small fraction of the mononuclear cell population in bone marrow (0.001-0.01%) [52].

At present, BM-MSC transplant techniques used to treat OA include BM-MSC scaffold implantation for isolated chondral defects and BM-MSC injectable techniques for isolated chondral defects and osteoarthritis. Scaffold implantation has produced a hyaline-like cartilage repair, pain and function improvement, and no donor site morbidity. BM-MSC injections have resulted in pain and functional improvement but have limited evidence of efficacy [11].

This review article has detailed how physical exercise improves the health of osteoarthritic joints and enhances the potential of BM-MSC for successful transplantation therapy by upregulating BM-MSC osteogenic and chondrogenic potential and downregulating BM-MSC adipogenic potential.

In light of the beneficial effects of exercise on articular cartilage chondrocytes, exercise may improve the results of autologous chondrocyte transplantation (ACT) in patients with OA. ACT involves the culturing of autologous chondrocytes and injecting them into the diseased joint of the donor/recipient [53]. Preclinical trials have shown that ACT is successful in producing hyaline-like cartilage regrowth [54-56] with reasonable long-term durability [57]. However, this method is associated with up to 40% dedifferentiation of chondrocytes during culturing and/or after the transplant [58]. Whether exercise will improve the outcome of ACT is yet to be determined.

Whether other joint preservation techniques are benefitted by exercise is also unknown. Osteoplasty involves drilling or punching of holes through the subchondral plate at the site of the chondral defect; this incites an inflammatory response which includes the mobilization of BM-MSC to the articular surface [59]. Since exercise has been shown to increase circulating levels of

BM-MSC, exercise done before and after osteoplasty has the potential to improve the results of this regenerative technique.

The evidence provided in this review supports a policy of recommending physical exercise for both BM-MSC donors and recipients. In addition, although not yet documented, exercise may benefit ACT donor/recipients and persons undergoing osteoplasty.

Recommending exercise for patients undergoing regenerative procedures has the added benefit of reducing their risks for ischemic cardiovascular disease, hypertension, diabetes mellitus, the metabolic syndrome, and certain forms of cancer [60].

The recommendation of the World Health Organization that adults undergo a minimum of 50 minutes of moderate intensity exercise three times weekly [10] should be sufficient to provide the aforementioned benefits.

8. Conclusion

Physical exercise done by both stem cell donors and recipients may improve the outcome of mesenchymal stem cell transplantation.

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