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# Exercise as an Adjuvant to Osteochondral Regeneration Therapy

*Opinion*

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## Opinion

There is increasing interest in using autologous chondrocyte implants (ACIs), matrix autologous chondrocyte implants (MACIs), and bone marrow-derived mesenchymal cell implants or injections in the surgical management of traumatic injuries, particularly of the tibiofemoral joint [1-7]. Recent studies have shown that physical exercise, which is known to improve osteoarthritis of the knee and hip [8-11], may serve as a valuable adjuvant in these osteochondral regeneration therapies [12].

Studies in rodents have shown that treadmill exercise upregulates the osteogenic potential of bone marrow derived mesenchymal stem cells (BM-MSC) including their expression of genes coding for alkaline phosphatase, caspase 3, osteocalcin, collagen I, sialoprotein and telomerase reverse transcriptase. Exercise also increases the proliferative capacity of BM-MSC and bone-marrow derived hematopoietic stem cell (BM-HSC) progenitors by upregulating their expression of colony-stimulating factor and granulocyte colony stimulating factor. In addition, exercise has been shown to enhance cartilage repair in rodents with experimentally induced osteochondral damage to their tibiofemoral joints [13-19].

Studies in humans have shown that physical exercise (ranging from short-term high intensity bicycling and treadmill exercises to running one-half marathons) upregulates BM-MSC and BM-HSC recruitment, enhances BM-MSC expression of osteogenic genes (runt-related transcription factor-2 (*Runx2*), muscle segment homobox gene (*MSx1*), and secreted phosphoprotein 1 (*SPP-1*) and their expression of chondrogenic genes SRY-Box 9 (*SOX9*) and collagen type II alpha-1 gene (*COL2A1*). Exercise also upregulates BM-MSC expression of micro-RNAs (miR) promoting osteoblast differentiation including miR-21-5p, miR-129-5p, miR-378-5p, and miR-188-5p, while downregulating their expression of miR-188-5p, an adipogenic miR.

Exercising subjects also increase their BM-MSC production of the bone and chondrocyte growth factors bone metamorphic protein 2 (BMP2) and BMP6 [20-23].

Exercise protocols designed for the treatment of osteoarthritis can be used prior to and after complete recovery from transplantation surgery. The American College of Sports Medicine (ACSM) guidelines indicate that training should include a minimum of 150 minutes of moderate intensity or 75 minutes of vigorous intensity aerobic exercises per week in bouts of at least 10 minutes. For resistance training, two sessions per week, with two sets of 8 to 12 repetitions at a load of 60% to 70% of one repetition maximum with a rest period of ≥48 hours between training sessions are indicated. Resistance training can produce favorable results independent of the type of equipment utilized (bands, weights, dynamometers), the type of exercise (isokinetic, isotonic), or the type of muscle action (isometric, eccentric, concentric) [24].

For postoperative patients, full weight bearing can start at 6 weeks with two weeks of 20% weight bearing coupled with continuous passive motion of 0-40 degree flexion exercises starting 12-24 hours post-surgery and continued until full recovery is achieved [24].

For healthy donors of BM-MSC I recommend prescribing an aerobic exercise regimen using the following guidelines:

a. Calculate the patient's age-based maximum heart rate (MHR) using the formula MHR=220-age.

b. Start the exercise program at 40-50% of MHR with weekly increments until the patient reaches 75-85% of MHR. The exercises should be done ≥30 minutes/day, 5 days a week.

In conclusion, it is my opinion that physical exercise done both by BM-MSC donors and recipients and by autologous chondrocyte donor-recipients may improve the outcome of osteochondral regeneration therapies while recognizing that further study in this area is warranted.

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