



Original Article

Effect of an Exercise Training Course and Bone Marrow-Derived Stem Cell injection on *Pax7* and *Myogenin* Expression in a Rat Model of Arthritis

Seyed Hassan Rasouli

(PhD Candidate) Exercise Physiology
Department, Sari Branch, Islamic Azad
University, Sari, Iran

Pravin Farzanegi

(PhD) Exercise Physiology
Department, Sari Branch, Islamic Azad
University, Sari, Iran

Hajar Abbaszadeh

(PhD) Exercise Physiology
Department, Sari Branch, Islamic Azad
University, Sari, Iran

Corresponding author: Pravin
Farzanegi

Tel: +989112230233

Email: parvin.farzanegi@gmail.com

Address: Department of Sport
Physiology, Sari Branch, Islamic Azad
University, Sari, Iran

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ABSTRACT

Background and objectives: Osteoarthritis is one of the most common arthritic diseases and a main cause of pain and disability. Simultaneous downexpression of *paired box 7* (*Pax7*) and *myogenin* genes, as indicators of satellite cells activation is evident in osteoarthritis. This study assessed effects of an exercise training course and stem cell injection on the expression of *Pax7* and *myogenin* in gastrocnemius muscle of rats with arthritis.

Methods: Thirty five male rats aged 6–8 weeks and weighing 250–300 g were divided into five groups: control, patient, exercise, mesenchymal stem cell (MSC), and exercise+MSC. Osteoarthritis was induced in rats by surgery. The training program consisted of 30 minutes of running on a non-slip treadmill at a speed of 16 m/min. The rats were injected with 1×10^6 cells/kg MSC. The expression of *Pax7* and *myogenin* was measured by real-time PCR. Data were analysed with SPSS (version 23) using one-way analysis of variance.

Results: Both *Pax7* and *myogenin* were significantly overexpressed in the exercise+MSC group compared to the patient group ($P < 0.001$).

Conclusion: The combination of MSC therapy and training had more positive effects on *Pax7* and *myogenin* expression compared to training and MSC therapy alone.

Keywords: Exercise, Stem cells, Pax7, Myogenin, Arthritis

INTRODUCTION

Osteoarthritis is one of the most common arthritic diseases and a main cause of pain and disability (1, 2). On the other hand, most patients with knee osteoarthritis are not willing to undergo knee surgery (3). Therefore, non-surgical methods such as injection of stem cells, platelet-rich plasma (4), corticosteroids (5) as well as exercise trainings (6) have been proposed for treatment of these patients. According to poor capability of chondrocytes in recovery of cartilage injuries, stem-cell-based treatments and cartilage tissue engineering can help treat damaged cartilage (7). Mesenchymal stem cells (MSCs) are therapeutic biological factors used for tissue regeneration and treatment of inflammatory diseases (8, 9). Intra-articular injection of MSCs was effective in treatment of osteoarthritis (8) and recovery of damaged cartilage in rats (7). Van Buul et al. observed that rats are able to weigh on affected leg after MSC therapy (10). It has been suggested that knee pain in patients is related to weakness of involved muscles, fatigue and joint instability (11). Additionally, the severity of disability in patient with osteoarthritis might be related to fatigue, dystrophy or injury in the involved muscles (12). Since one of the aims of treatment is reduction of pain, maintenance of joint mobility and minimizing disability in these patients (13), it is essential to find new approaches for reinforcement, growth and reconstruction of damaged or atrophied muscles in knee osteoarthritis patients.

Cellular studies reported that satellite cells can contribute to growth and reconstruction of damaged muscles (14). Muscle fibers continue to grow after birth by increasing the number of nuclei produced by stem cells (15). These cells are located between basement membrane and plasma membrane of myocytes (16). On the other hand, mono-nucleic cells located in the skeletal muscles have stem cells characteristics such as the proliferation and differentiation capability (17). In normal conditions, these cells are silent in mitotic division (18) but can be activated in response to homeostatic signals of satellite cells myofibers for production of myoblasts (16). For this purpose, multi-axis processes, such as activation of myogenic regulatory factors (Mrfs) and a group of chain transcription circle factors including myoD, Myf-5, and myogenin are required (14, 19-21).

Simultaneous expression of myoD and paired box 7 (Pax7) are known as important indicators of satellite cells activation (21). Increase in myoD is depended on Pax-3 and Pax-7. However, in the absence of Pax-3 and Pax-7, Myf-5 alone can activate and differentiate myogenin (21), but the produced satellite cell does not proliferate and apoptosis will occur (22). This shows that Pax-7 plays an important role in satellite cells behavior and reconstruction of skeletal muscles (23). It has been demonstrated that resistant (24) and aerobic training (25) can increase the activity of satellite cells by increasing myoD and Pax-7 levels. The present study aimed to assess the effect of an exercise training course and stem cell injection on expression of *Pax7* and *myogenin* genes in gastrocnemius muscle of rat models of arthritis.

MATERIALS AND METHODS

This experimental research was performed on 35 male Wistar rats aged 6-8 weeks weighing 250–300 g at the research center of Islamic Azad University, Sari Branch, Iran. The rats were divided into five groups: control, patient, exercise, MSC, exercise+MSC. Osteoarthritis was induced by surgery according to a method previously described by Malfait and Little (26). First, the rats were anesthetized with ketamine (30-50 mg/kg) and xylazine (3-5 mg/kg). After shaving the right knees, a 1 cm longitudinal incision was made to expose knee joint. The knee joint was immediately opened through lateral dislocation of the patella and patellar ligament. A longitudinally cut was provided in the knee joint capsule through the medial parapatellar incision. Lateral dislocation of the patella and patellar ligament was performed with forceps and then an incomplete incision was made through the medial meniscotibial ligament without articular cartilage and other ligaments injuries. Eventually, the knee joint capsule was closed with a 6-0 absorbable suture. The skin was closed with 6-0 silk suture. Examination of the histologic findings confirmed our osteoarthritis model.

Mesenchymal stem cells were isolated from bone marrow of the healthy rats after anesthesia with ketamine (30-50 mg/kg) and xylazine (3-5 mg/kg). Cells were cultured at density of 6 to 50 cells per cm², after partially filling of the surface of the culture plate; passage was done, and the above steps were

repeated until passage 3 or 4, until obtaining a pure set of cells. Isolated MSCs were incubated in DMEM medium with 20% fetal bovine serum overnight for selection of adherent cells.

Medium was refreshed every three days to remove untreated cells, and MSCs reached purity <90% after 3 to 4 passages. An injection of 10^6 cells per 2 μ l was infused into right knee joint of the rats by a syringe.

The rats were familiarized with the research environment and treadmill running at speed of 6-8 m/min and zero slope 5-10 min a day for four days. The main training course consisted of 25-29 min treadmill running without slope at speed of 15 m/min in the first week, which progressively reached the duration of 34-44 min and intensity of 16-18 m/min by the fourth week (Table 1). Also, warm up and cool down were performed five minutes before and after the training, respectively.

The rats were anaesthetized and sacrificed by intraperitoneal injection of ketamine (60 mg/kg) and xylazine (5 mg/kg) 48 hours after the last training session and following 12-14 hours fasting. Then, left knee joint tissue samples were collected and stored in 10% formaldehyde solution. After washing with distilled water and weighing, the isolated soleus and gastrocnemius muscles of the right leg were kept at -70 °C. After being powdered in liquid nitrogen, all freeze-dried tissues were homogenized in phosphate buffer saline (pH 7.0) and then centrifuged for 20 minutes at 12,000 rpm and 4°C. The solution was frozen at -80 °C to be used for chemical analysis by real time-polymerase chain reaction (RT-PCR).

RNA was extracted from the gastrocnemius muscle tissues using the RNX-Plus (SinaClon; RN7713C) Kit.

The quantity and quality of the extracted RNAs were assessed using Nanodrop ND-1000 spectrophotometer (Thermo Sci., Newington, NH). A complementary DNA (cDNA) was synthesized from RNA samples using RevertAid Reverse Transcriptase (Thermo science, Germany) at 42 °C for one hour using random hexamer primers (Thermo science, Germany). A Rotor-Gene 6000 (Corbett Research, Australia) thermocycler and Real Q-PCR 29 Master Mix Kit (Amplicon, Denmark) were used for the amplification process. The reaction solution included 5 μ l of master mix and 100 nmol of primers. The holding stage for RT-PCR was 95 °C 10 minutes. Cycle stages were as follows: 40 cycles at 95 °C for 15 seconds and at 60 °C for one minute. Sequence of the primers used is shown in table 2.

The mRNA levels of Pax7 and myogenin were normalized relative to the amount of *GAPDH* mRNA. Delta Ct (Δ CT) was calculated using the following formula: Δ CT= CT (target) - CT. Gene expression level was determined by the $2^{-\Delta$ Ct method.

After calculating mean and standard deviation of data, the Shapiro-Wilk test was carried out to assess normality of data distribution. The Levene's test was used in order to assess homogeneity of the variances. Changes in the study variables were assessed using one-way ANOVA and the post hoc Tukey test. All analyses were performed in SPSS software (version 23) at significance level of <0.05.

Table 1. Details of the training protocol performed by the training groups

Sessions	Exercise factors	First week	Second week	Third week	Forth week
First	Speed(m/min)	15	16	17	18
	Period(min)	25	30	35	40
Second	Speed(m/min)	15	16	17	18
	Period(min)	26	31	36	41
Third	Speed(m/min)	15	16	17	18
	Period(min)	27	32	37	42
Fourth	Speed(m/min)	15	16	17	18
	Period(min)	28	33	38	43
Fifth	Speed(m/min)	15	16	17	18
	Period(min)	29	34	39	44

Table 2. Sequence of the primers used in the RT-PCR experiment

Gene	Forward primer	Reverse primer
	5'-3'	5'-3'
<i>Pax7</i>	CCACATCCGTCACAAGATA	GAATCAAGTTCGGAAGAA
<i>Myogenin</i>	CAAGATTCTGTGCCGATA	CATGAACCCTGTGAGCAAT
<i>GAPDH</i>	AGACGATGACGGAAAAAGA	CATACTCAGCACCAGCACA

RESULTS

We observed histological changes in the articular joints of rats with osteoarthritis. As shown in figure 1, cartilage damage and synovitis are evident in the patients group compared to the control group.

There was a significant difference in Pax7 expression between the groups ($P < 0.001$). Pax7 expression was significantly higher in the exercise+MSC, MSC and exercise groups compared to the control group. In addition, Pax7 expression in the exercise+MSC group

was significantly higher compared to the MSC and exercise group ($P < 0.05$, Figure 2).

Myogenin expression differed significantly between the study groups ($P < 0.001$). Myogenin expression was significantly higher in the exercise+MSC, MSC and exercise groups compared to the patients groups. Moreover, myogenin expression was significantly higher in the exercise+MSC group compared to other groups ($P < 0.05$, Figure 3).

Figure 1: Histological changes of the articular joints in rats with osteoarthritis and healthy controls

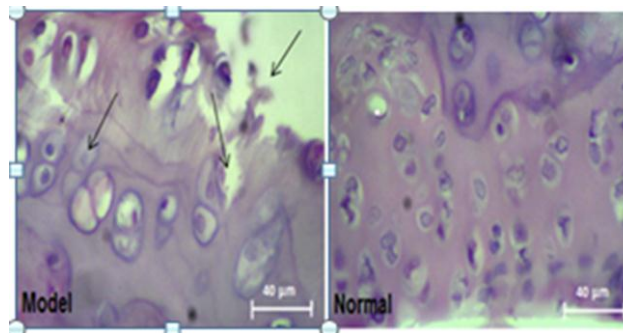


Figure 2. Mean Pax7 expression level in different study groups.

*significant difference compared to the patient group&: significant difference compared to the exercise+MSC group

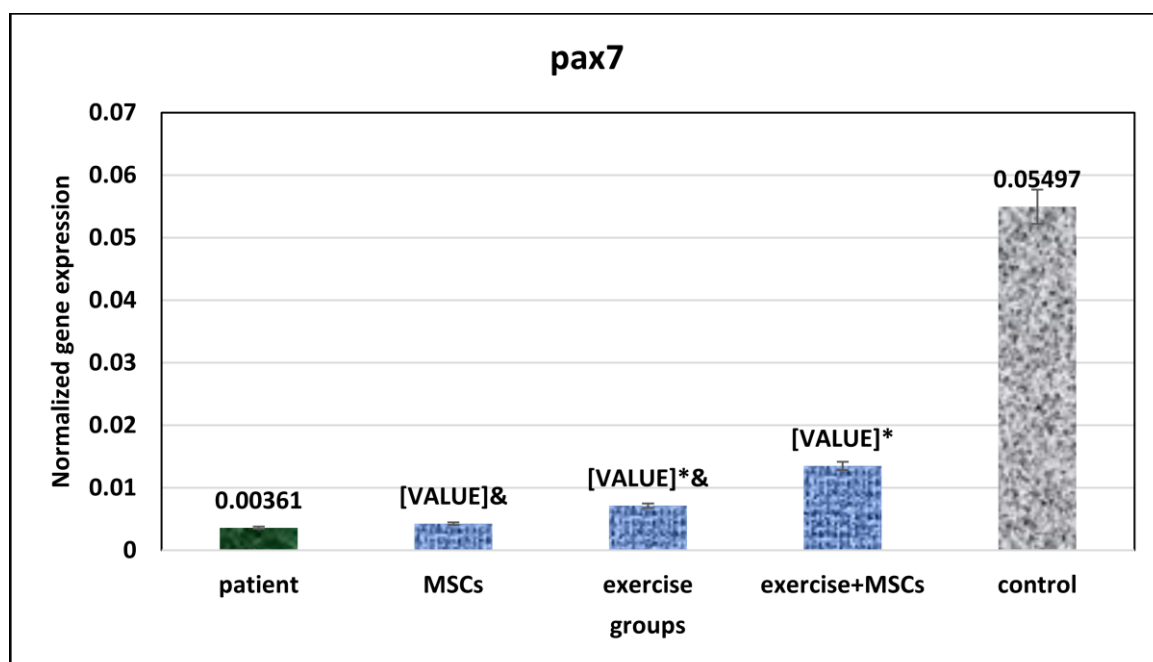
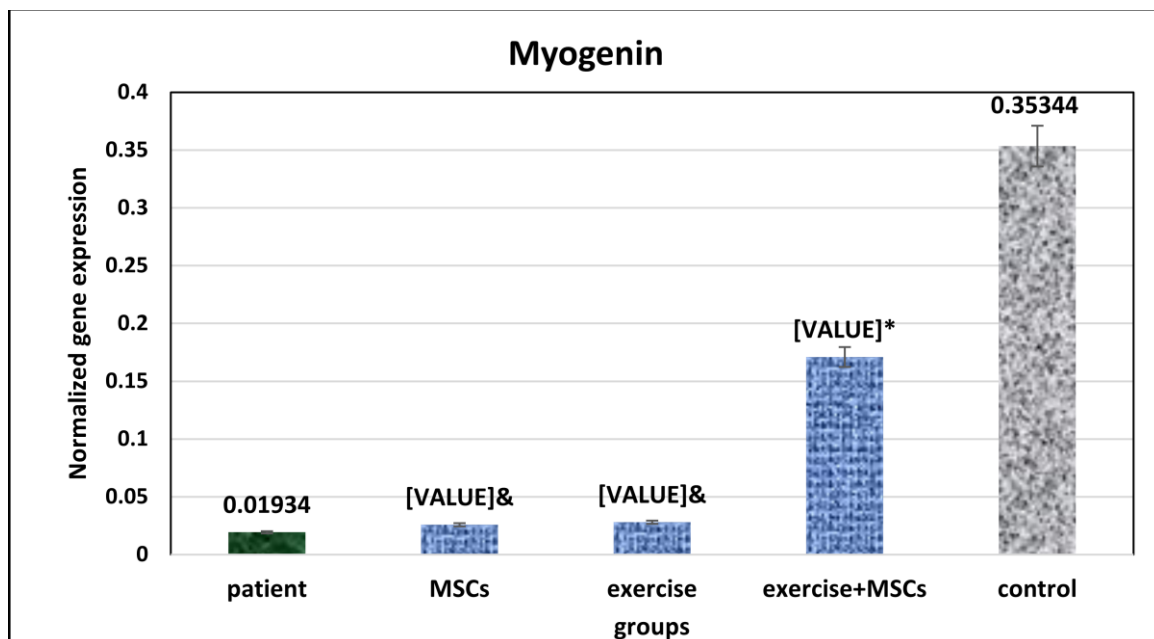


Figure 3. Mean myogenin expression level in the study groups.

*significant difference compared to the patient group&: significant difference compared to the exercise+MSC group



DISCUSSION

Our findings showed that osteoarthritis is accompanied with a significant reduction in Pax7 and myogenin expression in muscle tissue. This finding is in line with a previous study (27). The reduction in Pax7 and myogenin expression in muscle of animals with osteoarthritis might partly explain the mechanisms involved in osteoarthritis-induced muscle atrophy. In most pathologies, muscular atrophy is accompanied with chronic increase of inflammatory cytokines. Accordingly, muscle weakness indicates a concomitant imbalance in myofibrillar protein synthesis and proteolysis. Otherwise, myogenic stem cells also known as satellite cells, give mature skeletal muscles the ability to regenerate in response to muscle damage (28). The results of our study showed a decrease in myogenin expression in rats with osteoarthritis. According to previous studies, gene expression is reduced in atrophy as well as in inflammatory diseases (29). Myogenin is essential for the efficient activation of genes required for the final differentiation of myoblasts and the further synthesis of myoblasts into existing myofibers for muscle repair.

In addition, in the absence of myogenin, other muscle regulatory factors, such as myoD, cannot promote muscle formation due to impaired differentiation of satellite cells (27). Given the lack of change in Pax7 expression, the total number of satellite cells does not change in rats with osteoarthritis; therefore, decrease in satellite cell differentiation might play a main role in muscular dystrophy in the subjects. According to our findings and pathology of muscle weakness in osteoarthritis, Pax7 and myogenin can be considered as therapeutic targets. We found that MSCs and training separately can significantly increase Pax7 and myogenin expression in the gastrocnemius muscle of rats with osteoarthritis. However, the combination of two therapies was more effective. Several studies have evaluated the effect of training exercise and stem cell therapy on myogenic pathways and osteoarthritis. In 2016, Li et al. showed that MSCs can be maintained in the joint of rats for 10 weeks and can be effective for treatment of osteoarthritis (7). Fransen et al. showed that exercise significantly reduces pain and improves physical function (30). Gibbs et al. reported the positive effects of intra-articular injection of stromal bone marrow

and platelet-rich plasma along with exercise training in patients with osteoarthritis (31). In another study, a 5-day training program at moderate intensity on rats with experimental spinal cord injury significantly increased muscle growth factors and expression of myogenin, myoD, Mrf and Pax7 in the skeletal muscle of rats (32). Caldow et al. also reported that Myf-5, Pax7 and myoD increased significantly in response to 12-week full body resistant work out (33). In a study by Nederveen et al., a 16-week progressive resistant training program on individuals aged 25 years significantly increased Pax7 and myoD level compared to baseline values (34). Bone stem cells are able to participate in myogenesis and to differentiate into mesodermal cells, including myoblasts. In addition, MSCs also have pro-angiogenic potential that helps angiogenesis by directly differentiating into endothelial cells and/or supporting nerve cells for vascular reproduction, which are crucial for proper muscle function. In addition, the immunosuppressive properties of MSCs may inhibit the inflammatory process at the site of stem cell release. It is known that muscle degeneration is associated with chronic inflammation, which is associated with the active production of TNF- α by infiltrating M1 macrophages. Moreover, MSCs have the potential to convert M1-type inflammatory macrophages to the M2 phenotype, which is needed to improve and regenerate skeletal muscles and nerves. Some studies suggest that local release of MSCs to the muscles will provide an environmental support for myogenic precursors, a tendency to strengthen myogenic stem cells in damaged muscles and stimulate satellite cell migration (35).

CONCLUSION

The findings of this study indicate that osteoarthritis is accompanied with reduction in expression of Pax7 and myogenin in gastrocnemius muscle. The therapeutic effect of exercise and MSC therapy for improvement of knee osteoarthritis in rats is more profound when combined together. However, further studies at the protein level are necessary to evaluate the effects of exercise and MSC therapy on Pax7 and myogenin level in osteoarthritis.

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CONFLICTS OF INTEREST

All authors declare that there is no conflict of interest.

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