

**Original Article****Effects of a Single Session of Eccentric or Concentric Resistance Exercise on Relative Expression of BDNF, PAX7 and IGF-1 in Young Men**Mehrnaz Ghanizadeh¹, Mohammad Ali Azarbayjani^{2*}, Maghsoud Peeri³, Hasan Matin Homaei²

1- PhD Student, Department of Exercise Physiology, Islamic Azad University, Central Tehran Branch, Tehran, Iran.

2- Department of Exercise Physiology, Islamic Azad University, Central Tehran Branch, Tehran, Iran.

3- Department of Sports Physiology, Islamic Azad University, Central Tehran Branch, Tehran, Iran.

Received: August 2020

Accepted: October 2020

ABSTRACT

Background and Objectives: The aim of the present study was to investigate effects of a single session of eccentric or concentric resistance exercise on relative expression of BDNF, PAX7 and IGF-1 in healthy participants.

Materials and Methods: In a field trial, ten healthy young men were randomly assigned into two equal groups of concentric and eccentric contractions. Isokinetic contraction protocols included eccentric and concentric knee extensions with maximum power. The torques assigned were similar in the two groups. At the beginning and end of the exercise, biopsies of the lateral broad muscle tissue were collected to assess relative expression of BDNF, PAX7 and IGF-1.

Results: Statistically significant increases were seen in BDNF and PAX7 expression rates of the concentric exercise group ($p=0.021$ and $p=0.014$, respectively). Results showed that IGF-1 protein significantly increased after concentric and eccentric exercises ($p=0.005$ and $p=0.022$, respectively). In eccentric exercise group, BDNF and PAX7 expression rates increased significantly ($p=0.034$ and $p=0.034$, respectively).

Conclusions: Based on the findings, a single session of eccentric and concentric exercise changes factors involved in skeletal muscle strength and hypertrophy. In addition, these changes were totally more in eccentric contraction group, compared to concentric contraction group. It can be recommended to focus further on eccentric exercise to increase hypertrophy and muscle strength. Furthermore, these findings can be used to prevent obesity and type 2 diabetes.

Keywords: Muscular contractions, Metabolic effects, exercise modes, hypertrophy, Satellite cells

Introduction

In a variety of physiological and psychological disorders, neuromuscular biomarkers play important roles in responses of physiological systems to exercise and physical activities and are affected by nutritional and metabolic conditions (1–3). Regular physical activity can be used as a complementary therapy. In fact, amino acid (AA) turnover is a major factor in causing structural changes in muscles and is controlled by various muscle contractions as well as signal pathways (1). Pathological changes in neuromuscular biomarkers are associated with inflammation, obesity, insulin resistance and diabetes (4). Brain-derived neurotrophic factor (BDNF) has been identified as the most important regulator of neuronal differentiation, synaptic plasticity and cell death process (5). It plays important roles in learning and memory (6). The neurotrophic factor is the most important known trophic factor in the nervous system (7). The brain-derived neurotrophic factor, despite

its name, is not only present in the brain, but is naturally expressed in various tissues and cells, including retina, kidneys and prostate (8). Gharakhanlu et al. reported significant increases in IGF-1 levels in non-athlete men after plyometric exercises, some of which are eccentric in nature (9). Trained rats have been shown to include higher levels of BDNF in their veins, compared to that in inactive rats (9). Previous studies have suggested that increased BDNF levels strongly depend on intensity (10), duration (11) and frequency (12) of the activities. Moreover, BDNF treatment improves insulin sensitivity (13). Recent studies have shown close relationships between BDNF and satellite cell differentiation in skeletal muscles after muscle injuries (14). Bo Li et al. found that the BDNF levels were significantly lower in patients with T2DM, compared to those in control participants (15).

*Address for correspondence: Mohammad Ali Azarbayjani, Prof, Department of Exercise Physiology, Central Tehran Branch, Islamic Azad University, Tehran, Iran. E-mail address: m_azarbayjani@iauctb.ac.ir

Satellite cells are small mononuclear cells between the basement and cytoplasmic membranes that are activated in muscles, which form myoblasts in response to pressures from heavy exercises or blows and eventually turn into muscle fibers. In fact, these cells are specific stem cells that are found in almost every tissue and play roles in the normal growth, replacement and repair of tissues after chemical and mechanical damages. Numbers of satellite cells depend on animal species and age, types of muscle fibers and cell locations parallel to the fibers (16). Satellite cells are activated in response to physiological stimuli such as exercises and pathological conditions such as injuries and diseases to produce myoblasts capable of being synthesized and diagnosed. These cells can combine with existing muscle fibers, repair damaged muscle fibers or alternate with each other to form new muscle fibers (17). Scientific studies on effects of training on satellite cells have investigated effects of two types of resistance and endurance activities on these cells. Dungan et al. (2005) investigated effects of heavy resistance training and detraining on satellite cells in human skeletal muscles. These studies have shown that excessive pressures and strains and releases of inflammatory substances as well as growth factors produced by the resistance exercise activities can increase activities of the satellite cells and stimulate them to re-enter the cell cycle and proliferation (18). Based on the studies, satellite cells are regulated by PAX7, a cell cycle activating factor responsible for activating and regulating satellite cell reserves (19). Karyono et al. (2015) showed that moderate and low intensity trainings increased PAX7 expression, whereas high intensity training decreased PAX7 expression, compared to other groups (19). These results reveal that types of the exercise can affect PAX7 changes.

Insulin-like growth factors are a family of growth-promoting peptides that play important roles in tissue growth and development (20). The IGF-1 is a single-chain 70-AA polypeptide produced by the liver through stimulation, secreted by growth hormone and released into the bloodstream (21). Increases in IGF-1 and MGF were observed in young men after a one-week of strength training (22). However, they were no different mRNA expression of the both isoforms in the elderly (23). It was shown in a study with no strong associations with exercises that the eccentric part was essential for the positive expression of IGF-1 gene since only the concentric part of movements did not lead to positive expressions of this gene. Most studies of participants with no history of resistance training reported no changes in IGF-1 mRNA expression after exercises (24, 25). Nowadays, roles of muscle contraction manipulation in resistance training are reported important as most training and rehabilitation programs involve concentric and eccentric contractions during each repetition (1). Studies have shown that

eccentric exercise is metabolically lower than concentric exercise; however, it always leads to further muscle damages and greater inflammatory responses (26). Hortobagyi et al. (1996) concluded that extraversion activities were more adaptive relative to introversion activities (27) while Kay et al. (2000) achieved similar neurological adaptations in the two types of the exercises (28). Based on these data, potential roles of BDNF, PAX7 and IGF-1 in regulating human skeletal muscle masses and strength adaptations in response to resistance exercises are considered. Associations between neuromuscular biomarkers, inflammation, obesity and diabetes have been verified. Since studies on signaling pathways of the muscle growth factors in humans and their generalization to real groups can provide further accurate schemes of the molecular-cellular events and ultimately adaptability to coaches and sports scientists as well as further human generalizability compared to animal studies, this study was carried out on human samples. Therefore, the aim of the present study was to investigate relative expressions of BDNF, PAX7 and IGF-1 in response to eccentric and concentric exercises in young men.

Materials and Methods

Participants

From 18 to 30-year-old healthy active young men (people who carried out resistance exercises for at least three days for general health and physical activity promotion), ten men were randomly assigned into concentric ($n=5$) and eccentric ($n=5$) groups. The present trial study was a simple randomized individual study using a table of random numbers and correct concealment. Since this was based on regular activities, participants did not consume specific supplements or foods. National ID card numbers of the eligible participants were recorded and numbers of the participants were divided by ten. Considering numbers and the table of random numbers, participants were selected and grouped in intervention and control groups. Human studies must meet health needs of the population or community, where they are carried out. Ethical requirements are met when successful interventions or other benefits of such studies are made available to the public. To meet the ethical requirements, planning and management processes were carried out before the beginning of the study and monitored and assessed until the end of the processes, making results available to competent authorities and study populations. Competence and skills of the expert researchers and safe conditions of the study environment were approved by the ethics committees before and during the implementation. The ethics code of this study was IR.UT.SPORT.REC.1397.029 issued by the University of Tehran and registered at the Ministry of Health of the Islamic Republic of Iran. As soon as controversial issues were found in human commitments

and principles, study was discontinued. Receiving informed consents from the participants as well as ensuring their voluntariness and unconditional withdrawal from the study were integral parts of the researcher tasks.

The American College of Sports Medicine (ACSM) guidelines were used to assess health of the participants and minimize risks associated with their cardiovascular system. Participants were not undergone surgeries since six months prior to the study or on medications at the time of the study. After selection of the participants, objectives and procedures of the study were described to them and the participants signed consent forms for participating in the study. Demographic characteristics of the participants are presented in Table 3. Participants attended two sessions in the laboratory. Purpose of the first session was to familiarize the participants with the laboratory environment and the isokinetic system (Biodex Isokinetic Dynamometer, USA), measure their height and weight, explain Borg exercise pressure questionnaires to them and assess their torques. In the second session, participants randomly carried out one of the eccentric and concentric protocols at 8:00–9:00 AM. After assessing the 60° angle, isokinetic device was adjusted to impose the highest pressure on the athletes. Since the device is often used to rehabilitate people in post-recovery conditions, it did not impose the necessary pressure on the athletes to carry out the exhausting protocol of this study. Therefore, researchers should design exercise protocols including sets, repetitions and rest times for the athletes to reach exhaustion states. In this study, waves of force in isokinetic machine monitor existed and each repetition of the athletes was shown based on the value of the force used.

Concentric and eccentric exercise protocols

Participants rested for 10 min at each session and the procedures were reviewed to ensure that they understood how the exercise must be performed. Then, participants were seated on a dynamometer chair and settings were made to prepare the device. These settings included 90° orientation of tilt dynamometer, 90° of seat orientation, 85° of seat back tilt, 0–90° range of motion. Moreover, dynamometer rotation axis was selected on the sagittal plane with the line passing through the external condyle. Specific warming with the isokinetic system included two sets of five and the rest time between each set included 30 s. Then, participants carried out one of the two isokinetic muscle contraction protocols that was randomly assigned to their right foot. At the end of the exercise, the leg was fixed with no pressures until the biopsy was carried out. Biopsy of each participant was carried out 3–4 h after completion of the exercise protocol. During implementation of the protocol at the end of each set, the pressure perception was measured using Borg 20-point scale (RPE). Participants were asked to report a number on the Borg

scale after completing each set. When participants declared number 20, verbal encouragements urged him to continue further two sets and when they were unable to fully implement the protocol, the exercise was stopped. Isokinetic contraction protocols included eccentric and concentric knee extensions with maximum power and angular velocity of 60° per second. Torques assigned to each participant were assumed equal to match the workload in the two protocols with a rotational speed of 60° per second. Contractions maximally consisted of a 12 sets of ten repetitions for the right leg and a rest time of 30 seconds between each set. Obviously, eccentric exercise time was longer than concentric exercise one. Exercise protocols in eccentric and concentric groups are presented in Table 1.

Table 1. Exercise protocols in eccentric and concentric groups

Group	Number of sets	Number of movements	Rest between the sets
Eccentric	Max of 12 sets	10 repetitions	30 s at low speed
Concentric	Max of 12 sets	10 repetitions	30 s at high speed

Muscle tissue sampling

At the beginning and the end of the study, biopsies of the lateral broad muscle tissues were collected in a completely hygienic sterilized environment. The biopsy procedure was carried out in distal and proximal directions of the lateral broad muscles. Baseline biopsy specimens were collected by orthopedic surgeons for the first time and 3–4 h after the training in Baqiyatallah Hospital, Tehran, Iran (29). Dermal muscle biopsies (15–20 mg) were collected from the medial parts of the lateral broad muscles at the midpoint between the patella and the greater trochanter of the thigh with a depth of 1–2 cm based on the previously approved procedures. Biopsy site was cleaned and its hair was completely removed. Then, the site was washed with disinfectant soap and disinfected with alcohol. Furthermore, biopsy site was disinfected with betadine. A small area of the cleansed skin, approximately 2 cm in diameter, was anesthetized with a subcutaneous injection of 0.1 ml of lidocaine. Following anesthesia, a 16-inch needle aspiration biopsy specimen (Tru-Core I Biopsy Instrument, Techniques Device Technologies, USA) was placed at approximately 1-cm depth of the muscle tissue to extract the sample. After the initial biopsy, subsequent biopsy of the muscle tissue was extracted close to the previous site using pre-biopsy and needle depth markers. After muscle biopsies, adipose tissues were removed from the muscle samples. Samples were stored immediately at -80° C until use. In each of the two sessions, two muscle specimens were collected; from which, ten muscle specimens were totally collected for each group during the study and 20 specimens overall. In general, the muscle samples were collected at the baseline and 3–4 h after the exercises.

Relative expressions of BDNF and PAX7 in tissues

To assess the relative expressions of BDNF and PAX7 genes, tissue analysis was carried out in each group using real-time polymerase chain reaction (PCR). Primer design was first carried out; then, whole RNA was extracted from the tissues and converted to cDNA. The cDNA was amplified using PCR and analyzed for relative expressions of the highlighted genes. The RT-qPCR was used to verify quantitative relative expressions of the studied genes. The whole-cell RNA was extracted based on the manuals by the manufacturer using RNeasy lysis solution (Qiagen, Germany) and subjected to DNase I (Fermentas, USA) to ensure genomic DNA decontamination. Then, quality of the RNA was assessed using spectrophotometer (Qiagen DPI-1, Germany). Single-stranded cDNA was prepared using primers (Oligo dt MWG-Biotech, Germany) and reverse transcriptase enzymes (Fermentas, USA) based on the established protocols. Each PCR reaction was carried out using PCR master mix (Applied Biosystems, USA), SYBER Green and ABI Step One (Applied Biosystems, Sequences Detection Systems, USA) based on the manufacturer instruction. Generally, 40 cycles were used for each real-time PCR set using the following temperatures of 94° C for 20 s, 58–60° C for 30 s and 72° C for 30 s, respectively. Melting diagrams were recorded to check the accuracy of PCR reactions and assessed for each gene individually at each reaction time with negative control diagrams to check possible contaminations. Expression ratios of the genes were assessed using comparative method of the threshold cycle. Specific standard curves for each gene were plotted using at least five logarithmic concentrations diluted from positive controls. Target gene expression was normalized to the reference gene and the expression of healthy group genes was considered as calibrator. Formula E represents efficiency and is achieved using standard curves for the genes. The sequence of primers used in PCR is presented in Table 2. The reference gene included hGAP.

Table 2. Sequences of the primers used in real-time PCR

Gene	F/R	Primer (5' → 3')
BDNF	F	TTATTCCCACCATCCCACCTCT
	R	CCTCTTCCCTTTTCCCTTACCA
PAX7	F	CAAGCAGAAGAAGGAGTTGGAG
	R	CGAGATGAGTTAGAAGTTGATG
hGAP	F	GCAGGGATGATGTTCTGG
	R	CTTTGGTATCGTGAAGGAC

F/R, forward/reverse primers

The IGF-1 expression in tissues

Immunocytochemistry (ICC) was used to measure tissue IGF-1 expression. In general, this method is used to locate or detect subcellular locations of the specific antigens or proteins using labeled antibodies; in which, the

antigen-antibody complex is characterized by enzymatic markers and fluorescence dyes or radioactive detection markers. Therefore, cell suspensions were cultured on sterile gelatin lamellae. After 24 h, lamellae were washed with PBS and fixed in 4% paraformaldehyde for 4 min at refrigerated temperature. Lamellae were incubated at ambient temperature for 20 min after washing with PBS in 2-normal HCL. Then, lamellae were exposed to 0.3% Triton X-100 for 30 min. Triton permeates cell membranes to antibodies. Then, 10% goat serum was added to the cells for 1.5 h. Goat serum proteins cover non-specific antigenic sites, preventing non-specific reactions. Cells were incubated for 1 h with the primary diluted antibody at a ratio of 1:100 in PBS at refrigerated temperature using humid chamber. Use of parafilm and wet conditions prevented drying of the antibodies. Then, cells were washed twice with PBS and exposed to the secondary antibody conjugating with a dilution of 1:200 for 60 min at 37° C in darkness. After washing three times with PBS, PI or DAPI was used to the samples to stain the cell nuclei. Samples were then studied using fluorescent microscopy.

Statistical analysis

Descriptive and inferential statistical methods were used to analyze data. Descriptive statistics were used to calculate the mean and standard deviation (SD) of the data and inferential statistics were used to compare the groups. Kolmogorov-Smirnov test was used to check the normality of data distribution. Significant t-test ($p \leq 0.05$) was used to compare within-group means. Covariance test was used to compare the two groups. Analysis of covariance (ANCOVA) was used to neutralize effects of the pre-test. The SPSS Software v.21 (IBM Analytics, USA) was used to analyze data and Excel 2013 to design charts. A summary of the statistical results is presented in Tables 3 and 5.

Results

Descriptive data linked to demographic indicators of the participants are presented in Table 3.

Table 3. Demographic indicators of the participants in the two groups

Exercise group	Variable	Mean ±SD
Concentric	Weight (kg)	71.50±8.16
Eccentric	Weight (kg)	72.10±9.61
Concentric	BMI (kg/m ²)	23.45±2.26
Eccentric	BMI (kg/m ²)	24.26±1.97
Concentric	Height (cm)	178.80±4.26
Eccentric	Height (cm)	176.26±4.67
Concentric	Age (year)	26.76±3.45
Eccentric	Age (year)	25.15±2.68

SD, standard deviation

Based on the results of Table 5, significant differences were seen between the pre and post-test values of BDNF in concentric and eccentric exercise groups ($p \leq 0.05$). However, no significant differences were seen between the pre and post-test values of PAX7 in concentric and eccentric exercise groups (Table 5). Significant differences were observed between the pre and post-test values of IGF-1 in concentric and eccentric exercise groups ($p \leq 0.05$). Covariance test was used to assess effects between the groups. To homogenize selected samples and eliminate interfering factors, paired test was used to calculate homogeneity of the samples before pre and post-tests. In Table 5, all values are significant based on the reported p values and their trend was ascending in the two groups. Results of the ANCOVA table show that there is a significant difference between the two groups in IGF-1 post-test values ($p = 0.014, F = 26.227$). Based on the results of Table 5, the F value of the intervening variable (BDNF pre-test) is 0.089 and the significance value is $p = 0.775$, therefore it can be said that the variable is selected correctly. In addition, results of the ANCOVA table show that there is no significant difference between the various groups in BDNF post-test values ($p = 0.439$ and $F = 0.673$). Based on the results of Table 5, the F value of the intervening variable (PAX7 pre-test) is 0.508 and the significance level is $p = 0.947$, therefore it can be said that the variable is selected correctly. In addition, results of the ANCOVA table show that there is no significant difference between the various groups in PAX7 post-test values ($p = 0.336$ and $F = 1.068$). Eccentric exercise group ($p \leq 0.05$). Nevertheless, no significant differences were reported between pre and post-test PAX7 levels of the concentric and eccentric exercise groups ($p \geq 0.05$). Significant differences were seen between pre and post-test IGF-1 levels in concentric and eccentric exercise groups ($p \leq 0.05$). Protein levels in pre and post-tests in the lateral

broad muscles of the two groups using fluorescence microscopy are shown in Fig. 1.

Table 4. Results of the analysis of covariance in post-test values of BDNF, PAX7 and IGF-1 for the effect. assessment of the groups

Variable	Source	DF	Mean squares	F-value	p-value
BDNF	Pre-test BDNF	1	-009E1.262	0.089	0.775
	Group	1	-009E9.588	0.673	0.439
	Error	7	-008E1.425		
	Total	10			
PAX7	Pre-test PAX7	1	0.005	0.508	0.947
	Group	1	1.135	1.068	0.336
	Error	7	1.063		
	Total	10			
IGF1	Pre-test IGF1	1	34.085	6.138	0.089
	Group	1	145.908	26.275	0.014
	Error	7	5.553		
	Total	10			

DF, degrees of freedom

Table 5. Results of the dependent sample t-test to compare the means of pre and post-test BDNF, PAX7 and IGF-1 levels in the two groups

Variable	Exercise group	Mean difference	t	DF	p-value
BDNF	Concentric	-0.00014	-3.702	4	0.021
	Eccentric	-0.00020	-3.159	4	0.034
PAX7	Concentric	-0.0560	1.789	4	0.014
	Eccentric	-0.721	-1.178	4	0.034
IGF-1	Concentric	-37.406	-13.735	4	0.005
	Eccentric	-33.386	-6.598	4	0.022

DF, degrees of freedom

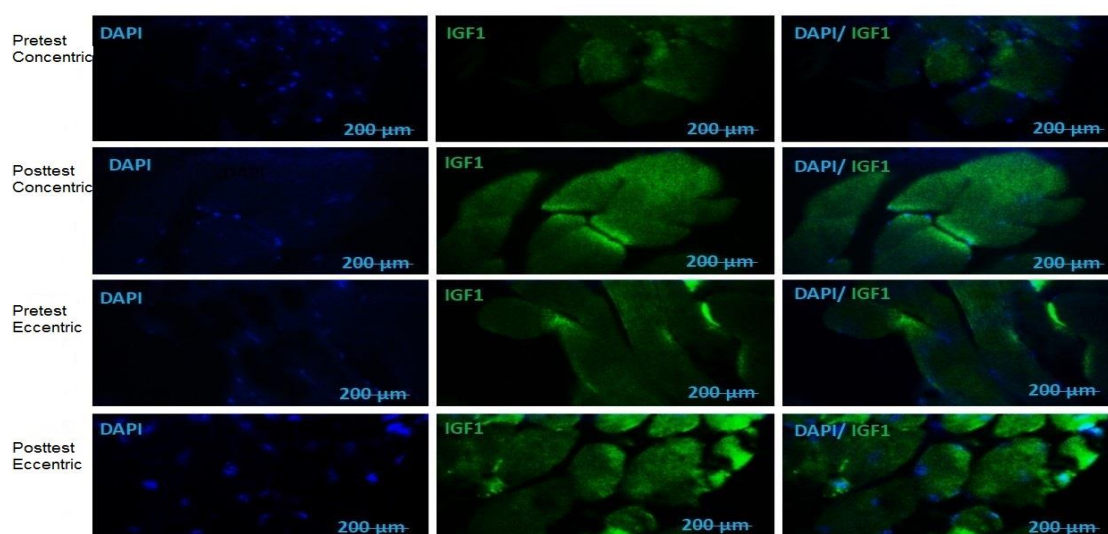


Figure 1. Illustration of IGF-1 protein levels in pre and post-tests in lateral broad muscles of the two groups using fluorescence microscopy. The IGF-1 staining by DAPI in eccentric and concentric groups before and after the tests. Photos are representative of vastus lateralis muscle samples from pre and post-test biopsies of a participant stained with anti-AGF-1.

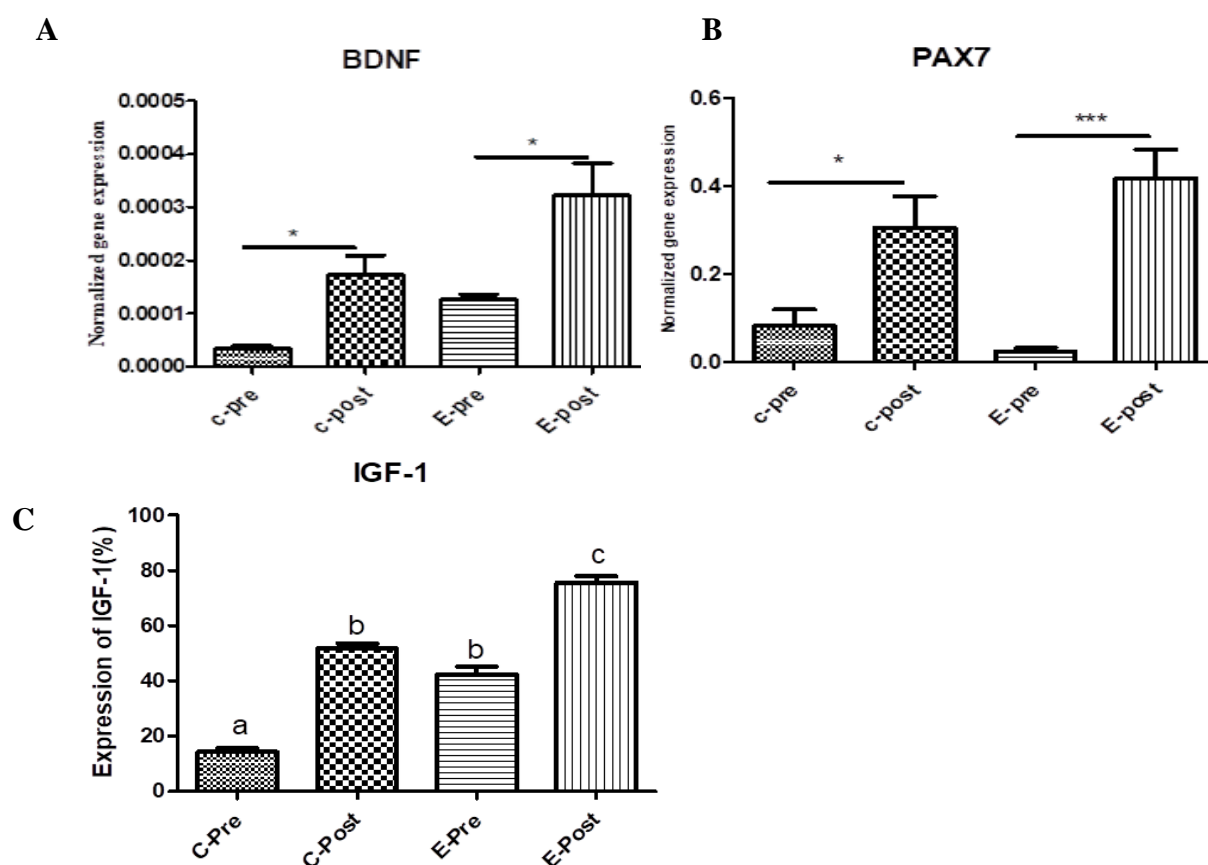


Figure 2. Relative expressions of BDNF (A), PAX7 (B) and IGF-1 (C) in pre and post-tests of the two groups. *Significant differences between the pre and post-test levels ($p \leq 0.05$). No significant differences were seen between the pre and post-test levels of BDNF and PAX7 in concentric and eccentric exercise groups based on the statistical analysis ($p \leq 0.05$). Furthermore, no significant differences were seen between the pre and post-test levels of IGF-1 in concentric and eccentric exercise groups ($p \geq 0.05$).

Discussion

The aim of the present study was to assess effects of a single session of eccentric or concentric resistance exercise on relative expressions of BDNF, PAX7 and IGF-1 in healthy participants. Although this issue is widely verified and empirically accepted based on the principles of repetition, little is known about the molecular mechanisms underlying RE training-induced adaptations. One hypothesis is that following each exercise session, an acute transcriptional response occurs of higher magnitudes following the successive sessions (5). This results in accumulation of cognate proteins (gain of function); thereby, enabling or augmenting key biological processes needed for the adaptation (9, 16, 40). Although this theoretically sounds, principles of repetition during RE training should be explained at various levels (e.g., DNA modifications, mRNA levels, protein levels and posttranslational modifications). Recent high-throughput studies have elucidated transcriptional responses to RE training (26). The fact that muscle contractions can affect muscle hypertrophy due to AA turnover is another metabolic aspect of the present study (1). In the present

study, significant differences were seen between pre and post-test BDNF levels of the concentric and eccentric exercise groups. Furthermore, significant differences were seen between pre and post-test PAX7 levels of the concentric and eccentric exercise groups. Significant differences were also observed between pre and post-test IGF-1 levels in concentric and eccentric exercise groups.

It has been shown that metabolic efficiency of the eccentric contractions is lower than that of concentric and isometric contractions (1). This is affected by various factors that trigger neuromuscular signaling pathways. Two mechanisms may generally interact, obesity-related insulin resistance and decreased insulin signaling in the brain may be exacerbated by the chronic peripheral and CNS inflammatory environment associated with obesity. These changes verify changes of IGF-1 in the present study. In fact, IGF-1 is a single-chain 70-AA polypeptide that is produced due to the growth hormone through liver stimulation and is secreted into the bloodstream (21). In the present study, responses to IGF-1 and its expression in eccentric and concentric resistance exercises in healthy

participants were investigated. Results showed that intragroup changes of IGF-1 after one session of exercise were significant in eccentric and concentric groups. Intergroup changes showed statistical differences between the two groups. Researchers have reported increased IGF-1 mRNA expression in untrained individuals at various time points after exercises (25, 30, 31). In trained participants, IGF-1 expression increased after exercises. After chronic exercises, baseline IGF-1 levels were upregulated (32). In addition, studies showed that 24 and 48 h after acute exercises, positive IGF-1 upregulation occurred in trained individuals. In untrained individuals, this positive upregulation was not observed (24, 25). The IGF-1 receptor expression was upregulated 2 h after exercises, suggesting that this upregulation was likely to occur more frequently in slow-stressed cords (31). The IGF-1 receptor expression up to 6 h after exercises suggested that the IGF-1 system might be involved in resistance exercise adaptations (33). In a study with no strong correlations with intensity of exercises, the eccentric part was shown essential for positive IGF-1Ea expressions, only the concentric part of movements did not lead to positive expressions of this gene (34). Despite increasing total volumes of low intensity exercises, IGF-1R activation increased by 60–65 and 80–85% of one maximum repetition (1RM) 2 and 6 h after exercises (33). Similarly, IGF-1Ea and MRF mRNA expressions increased equally by 60–65 and 80–85% of 1RM 2 h after exercises (31). Based on specific effects of the contraction types in this study, the eccentric exercise relatively included higher effects on IGF-1 isoform changes. Bamman et al. (2001) investigated IGF-1 expression 48 h after eccentric and concentric exercises in young participants. Results of the study revealed increases only in eccentric contractions (35). In contrast, Adam et al. (2004) reported that prolonged eccentric exercises included no effects on IGF-1Ea and MGF levels in muscles of female rats, whereas increases were reported in concentric and isometric contractions (36).

Differences in nature of the stimulation types appear to contribute to differences in results. It is noteworthy that differences were seen between the groups in the present study. Muscle damages have been shown to increase IGF-1 in human and rat muscles (37, 38). Exercises in this study appear to trigger injuries, which did not occur in Adam et al. study. Results showed that the relative expression of BDNF in the eccentric group was higher than that in the concentric group with no significant differences. Pedard et al. (2018) showed that exercise-induced increases in BDNF depended on the contraction types (39). Goekint et al. (2010) (40) and Yarrow et al. (2010) (41) were the first researchers to study BDNF responses induced by resistance trainings. Yarrow et al. reported a 32% increase in serum BDNF following resistance trainings, whereas Goekint et al. showed a 4% change in BDNF levels following acute

resistance trainings. Goekint et al. stated that the intensity of their resistance trainings was low with relatively long rest periods. Yarrow et al. investigated resistance trainings at two various intensities, one consisted of four sets with six repetitions of concentric and eccentric contractions and the other one consisted of three sets of six repetitions with concentric and eccentric contractions and 100% of one maximal repetition (1RM) (41). The researchers showed temporary increases in BDNF in the two groups, independent of exercises. Groups were similar according to the volume of exercises. It is likely that acute strength trainings can stimulate peripheral BDNF under conditions, where the exercise loads are sufficiently intense. Therefore, it can be concluded that the exercise protocols used in the eccentric group of the current study include good intensities to stimulate production of this trophic factor and are good reasons for significant increases in post-exercise BDNF levels. A few studies have assessed the PAX7 changes. In the present study, results showed significant increases in PAX7 in the two groups. These changes were greater in eccentric group, compared to the baseline. In a study, Karyono et al. (2018) investigated effects of endurance trainings on PAX7 expression changes in rats. Their results showed that low, moderate and high intensity trainings resulted in increased PAX7, which was associated with satellite cells (19). Several studies on satellite cells have investigated the expression of PAX7. The PAX7 is a transcription factor in satellite cells close to the nucleus and is essential for myogenic and satellite cell regenerations. Sophie et al. (2014) reported that exercise training did not reservedly increase satellite cells but rather increased cells that were activated due to the regeneration of muscle fibers (42). However, Schefer et al. (2010) showed that satellite cells per muscle fiber increased after moderate intensity trainings (43). Eileton et al. showed that physical activity and increased BDNF levels improved insulin sensitivity (13). In another study, Bo Lee et al. found that mean serum BDNF levels were significantly lower in patients with T2DM than in controls (15). In the present study, it was shown that eccentric and concentric exercises increased expression of PAX7 in lateral broad muscles. Several adaptations such as increased strength and lean mass are resulted from repetitive resistance exercises due to the high degrees of skeletal muscle flexibility in response to exercise pressures. Various exercise stimuli in resistance exercises can elicit various molecular responses associated with specific adaptations of the skeletal muscles to the types of resistance exercises. Prescribing resistance program should be carried out with careful considerations of manipulating variables. Exercise variables include intensity, volume and time under stress. Hence, manipulation of these variables can affect the results.

Conclusion

In general, a session of eccentric or concentric exercise leads to significant changes in factors involved in strength and hypertrophy of the skeletal muscles. Since pathological changes in neuromuscular biomarkers are associated with inflammation, obesity, insulin resistance and diabetes, these exercises can be used to prevent these problems, especially in elderly people with sarcopenia. Moreover, these changes are generally greater in eccentric contraction than concentric contraction. Therefore, it can be recommended that athletes who tend to increase muscle hypertrophy and strength should further focus on concentric exercises.

Acknowledgement

This manuscript is a part of a PhD dissertation. The authors would like to express their gratitude to officials within the University of Tehran and Baqiyatallah Hospital, who facilitated the current study. All the expenses within the current dissertation were paid personally and no financial supports were provided by other organizations.

Financial disclosure

The authors declare no conflict of interest.

References

1. Franchi MV, Reeves ND, Narici MV. Skeletal muscle remodeling in response to eccentric vs. concentric loading: morphological, molecular, and metabolic adaptations. *Frontiers in physiology*. 2017;8:447.
2. Figueroa JT, Vera S, Aranzález LH, Mockus I. Nutritional condition and IGF-1 and IGF-1R serum concentrations in students aged 7 to 9 attending two educational institutions. *Revista de la Facultad de Medicina*. 2016;64:439-45.
3. Numakawa T, Richards M, Nakajima S, Adachi N, Furuta M, Odaka H, et al. The Role of Brain-Derived Neurotrophic Factor in Comorbid Depression: Possible Linkage with Steroid Hormones, Cytokines, and Nutrition. *Frontiers in Psychiatry*. 2014;5(136).
4. Spielman LJ, Little JP, Klegeris A. Inflammation and insulin/IGF-1 resistance as the possible link between obesity and neurodegeneration. *Journal of Neuroimmunology*. 2014;273(1):8-21.
5. Lou SJ, Liu JY, Chang H, Chen PJ. Hippocampal neurogenesis and gene expression depend on exercise intensity in juvenile rats. *Brain research*. 2008;1210:48-55.
6. Gomez-Pinilla F, Vaynman S, Ying Z. Brain-derived neurotrophic factor functions as a metabotrophin to mediate the effects of exercise on cognition. *European Journal of Neuroscience*. 2008;28(11):2278-87.
7. Ploughman M. Exercise is brain food: the effects of physical activity on cognitive function. *Developmental neurorehabilitation*. 2008;11(3):236-40.
8. Ernfors P, Kucera J, Lee KF, Loring J, Jaenisch R. Studies on the physiological role of brain-derived neurotrophic factor and neurotrophin-3 in knockout mice. *The International journal of developmental biology*. 1995;39(5):799-807.
9. Banoujaafar H, Monnier A, Pernet N, Quirie A, Garnier P, Prigent-Tessier A, et al. Brain BDNF levels are dependent on cerebrovascular endothelium-derived nitric oxide. *The European journal of neuroscience*. 2016;44(5):2226-35.
10. de Almeida AA, Gomes da Silva S, Fernandes J, Peixinho-Pena LF, Scorza FA, Cavalheiro EA, et al. Differential effects of exercise intensities in hippocampal BDNF, inflammatory cytokines and cell proliferation in rats during the postnatal brain development. *Neuroscience letters*. 2013;553:1-6.
11. Sheikhzadeh F, Etemad A, Khoshghadam S, Asl NA, Zare P. Hippocampal BDNF content in response to short- and long-term exercise. *Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology*. 2015;36(7):1163-6.
12. Costa MS, Ardais AP, Fioreze GT, Mioranzzza S, Botton PH, Souza DO, et al. The impact of the frequency of moderate exercise on memory and brain-derived neurotrophic factor signaling in young adult and middle-aged rats. *Neuroscience*. 2012;222:100-9.
13. Eyileten C, Kaplon-Cieslicka A, Mirowska-Guzel D, Malek L, Postula M. Antidiabetic Effect of Brain-Derived Neurotrophic Factor and Its Association with Inflammation in Type 2 Diabetes Mellitus. *J Diabetes Res*. 2017;2017:2823671.
14. McKay BR, Nederveen JP, Fortino SA, Snijders T, Joannis S, Kumbhare DA, et al. Brain-Derived Neurotrophic Factor is Associated with Human Muscle Satellite Cell Differentiation in Response to Muscle Damaging Exercise. *Applied Physiology, Nutrition, and Metabolism*. 2019(ja).
15. Li B, Lang N, Cheng ZF. Serum Levels of Brain-Derived Neurotrophic Factor Are Associated with Diabetes Risk, Complications, and Obesity: a Cohort Study from Chinese Patients with Type 2 Diabetes. *Mol Neurobiol*. 2016;53(8):5492-9.
16. Snijders T, Leenders M, de Groot L, van Loon LJ, Verdijk LB. Muscle mass and strength gains following 6 months of resistance type exercise training are only partly preserved within one year with autonomous exercise continuation in older adults. *Experimental gerontology*. 2019;121:71-8.
17. Snijders T, Nederveen JP, Bell KE, Lau SW, Mazara N, Kumbhare DA, et al. Prolonged exercise training improves the acute type II muscle fibre satellite cell response in healthy older men. *The Journal of physiology*. 2019;597(1):105-19.
18. Dungan CM, Murach KA, Frick KK, Jones SR, Crow SE, Englund DA, et al. Elevated myonuclear density during skeletal muscle hypertrophy in response to training is reversed during detraining. *American Journal of Physiology-Cell Physiology*. 2019;316(5):C649-C54.
19. Mustofa KM, Agustina Tri Endharti. Effect of Endurance Treadmill Training on mIGF-1 Expression and PAX7 Satellite Cell in Rat Muscle Tissues. *Research Journal of Life Science*. 2018;5(2):(83-8).
20. Yakar S, Rosen CJ, Beamer WG, Ackert-Bicknell CL, Wu Y, Liu JL, et al. Circulating levels of IGF-1 directly regulate bone growth and density. *The Journal of clinical investigation*. 2002;110(6):771-81.
21. Harridge SD. Plasticity of human skeletal muscle: gene expression to in vivo function. *Experimental physiology*. 2007;92(5):783-97.
22. Xiao W, Chen P, Wang R, Dong J. Overload training inhibits phagocytosis and ROS generation of peritoneal macrophages:

- role of IGF-1 and MGF. *European journal of applied physiology*. 2013;113(1):117-25.
23. Hameed M, Lange K, Andersen J, Schjerling P, Kjaer M, Harridge S, et al. The effect of recombinant human growth hormone and resistance training on IGF-I mRNA expression in the muscles of elderly men. *The Journal of physiology*. 2004;555(1):231-40.
 24. Ahtiainen JP, Lehti M, Hulmi JJ, Kraemer WJ, Alen M, Nyman K, et al. Recovery after heavy resistance exercise and skeletal muscle androgen receptor and insulin-like growth factor-I isoform expression in strength trained men. *Journal of strength and conditioning research*. 2011;25(3):767-77.
 25. Bamman MM, Petrella JK, Kim JS, Mayhew DL, Cross JM. Cluster analysis tests the importance of myogenic gene expression during myofiber hypertrophy in humans. *Journal of applied physiology*. 2007;102(6):2232-9.
 26. Koskinen SO, Lehti M. Molecular and Cellular Markers in Skeletal Muscle Damage after Acute Voluntary Exercise Containing Eccentric Muscle Contractions. *Muscle Cell and Tissue: Current Status of Research Field*. 2018:19.
 27. Hortobagyi T, Barrier J, Beard D, Braspeninx J, Koens P, Devita P, et al. Greater initial adaptations to submaximal muscle lengthening than maximal shortening. *Journal of applied physiology*. 1996;81(4):1677-82.
 28. Kay D, St Clair Gibson A, Mitchell MJ, Lambert MI, Noakes TD. Different neuromuscular recruitment patterns during eccentric, concentric and isometric contractions. *Journal of electromyography and kinesiology : official journal of the International Society of Electrophysiological Kinesiology*. 2000;10(6):425-31.
 29. Dieli-Conwright CM, Kiwata JL, Tuzon CT, Spektor TM, Sattler FR, Rice JC, et al. Acute Response of PGC-1 α and IGF-1 Isoforms to Maximal Eccentric Exercise in Skeletal Muscle of Postmenopausal Women. *Journal of strength and conditioning research*. 2016;30(4):1161-70.
 30. McKay BR, O'Reilly CE, Phillips SM, Tarnopolsky MA, Parise G. Co-expression of IGF-1 family members with myogenic regulatory factors following acute damaging muscle-lengthening contractions in humans. *The Journal of physiology*. 2008;586(22):5549-60.
 31. Wilborn CD, Taylor LW, Greenwood M, Kreider RB, Willoughby DS. Effects of different intensities of resistance exercise on regulators of myogenesis. *Journal of strength and conditioning research*. 2009;23(8):2179-87.
 32. Kvorning T, Andersen M, Brixen K, Schjerling P, Suetta C, Madsen K. Suppression of testosterone does not blunt mRNA expression of myoD, myogenin, IGF, myostatin or androgen receptor post strength training in humans. *The Journal of physiology*. 2007;578(2):579-93.
 33. Taylor LW, Wilborn CD, Kreider RB, Willoughby DS. Effects of resistance exercise intensity on extracellular signal-regulated kinase 1/2 mitogen-activated protein kinase activation in men. *Journal of strength and conditioning research*. 2012;26(3):599-607.
 34. Bamman MM, Shipp JR, Jiang J, Gower BA, Hunter GR, Goodman A, et al. Mechanical load increases muscle IGF-I and androgen receptor mRNA concentrations in humans. *American journal of physiology Endocrinology and metabolism*. 2001;280(3):E383-90.
 35. Bamman MM, Shipp JR, Jiang J, Gower BA, Hunter GR, Goodman A, et al. Mechanical load increases muscle IGF-I and androgen receptor mRNA concentrations in humans. *American journal of physiology-endocrinology and metabolism*. 2001;280(3):E383-E90.
 36. Adams GR, Cheng DC, Haddad F, Baldwin KM. Skeletal muscle hypertrophy in response to isometric, lengthening, and shortening training bouts of equivalent duration. *Journal of applied physiology*. 2004;96(5):1613-8.
 37. Hather B, Tesch P, Buchanan P, Dudley G. Influence of eccentric actions on skeletal muscle adaptations to resistance training. *Acta Physiologica Scandinavica*. 1991;143(2):177-85.
 38. Singh MAF, Ding W, Manfredi TJ, Solares GS, O'Neill EF, Clements KM, et al. Insulin-like growth factor I in skeletal muscle after weight-lifting exercise in frail elders. *American Journal of Physiology-Endocrinology And Metabolism*. 1999;277(1):E135-E43.
 39. Pedard M, Cefis M, Ennequin G, Quirie A, Garnier P, Prigent-Tessier A, et al. Brain-derived Neurotrophic Factor Pathway after Downhill and Uphill Training in Rats. *Medicine and science in sports and exercise*. 2019;51(1):27-34.
 40. Goekint M, De Pauw K, Roelands B, Njemini R, Bautmans I, Mets T, et al. Strength training does not influence serum brain-derived neurotrophic factor. *European journal of applied physiology*. 2010;110(2):285-93.
 41. Yarrow JF, White LJ, McCoy SC, Borst SE. Training augments resistance exercise induced elevation of circulating brain derived neurotrophic factor (BDNF). *Neuroscience letters*. 2010;479(2):161-5.
 42. Joanisse S, Gillen JB, Bellamy LM, McKay BR, Tarnopolsky MA, Gibala MJ, et al. Evidence for the contribution of muscle stem cells to nonhypertrophic skeletal muscle remodeling in humans. *The FASEB Journal*. 2013;27(11):4596-605.
 43. Shefer G, Rauner G, Yablonka-Reuveni Z, Benayahu D. Reduced satellite cell numbers and myogenic capacity in aging can be alleviated by endurance exercise. *PloS one*. 2010;5(10):e13307.