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Effect of combined training on gene expression of nuclear factor-κB and Sirtuin 1 in fast and slow twitch muscles in elderly male rats

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Abstract

Background: The aim of this study is to investigate the effects of ten weeks of combined training on the gene expression of nuclear factor-κB and sirtuin 1 in fast and slow twitch muscles of aged male rats.

Methods: Sixteen rats, each 24 months old, were randomly divided into two groups: combined training and control (Eight rats per group). Combined exercises were performed four sessions per week, including two days of endurance and two days of resistance. The exercises took place in a container measuring 50x50x100 cm, filled with water maintained at 30±1°C. On the first day, the animals swam for five minutes in water at a height equal to 100% of their body length, without weights. On the second and third days, the rats swam for 10 minutes with the water height equal to 120% of their body length. On the fourth and fifth days, they swam for 15 minutes with the water height at 140% of their body length, which remained constant during the study period. Data were analyzed using two-way analysis of variance with SPSS version 22 software, with the significance level at $P \leq 0.05$.

Results: After ten weeks of combined training, a significant difference was observed in the gene expression of nuclear factor-κB and sirtuin 1 between the training and control groups (P=0.001 for both).

Conclusion: According to the results of this research, performing combined exercises in water with appropriate intensity and duration can regulate inflammatory and anti-inflammatory pathways, thereby strengthening muscles and reducing muscle wasting and atrophy in the elderly.

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Introduction

Aging is a biological phenomenon in which the structure and function of the human body decline with age (1). One of the most significant changes that occur in the human body with aging is the breakdown and loss of muscle mass, leading to a dramatic reduction in the volume and size of skeletal muscle, a condition known as "sarcopenia" (2). The sirtuin family comprises seven members, sirtuin 1-7 (SIRT1-7) (3). Sirtuin 1 (SIRT1) is a nicotinamide adenine dinucleotide (NAD+)-dependent protein that plays a crucial role in strengthening the antioxidant system, regulating and suppressing inflammation, aging, cellular autophagy, cancer, and dealing with the effects of oxidative stress on various body tissues (4). One of the key indicators inhibited by elevated SIRT1 levels is NF-κB, a major transcription factor involved in regulating inflammatory responses that can activate innate and acquired immune responses to traumatic factors (5). This transcription factor is not only the primary regulator of inflammatory responses but also regulates several homeostatic responses, including apoptosis, autophagy, and tissue atrophy pathways (6).

Research has shown that long-term aerobic exercise facilitates the SIRT1 protein pathway in aged mice. Aerobic exercise increases the expression of SIRT1 and thus inhibits the NF-κB pathway (7). Studies indicate that various types of exercise (Resistance and aerobic) are considered healthy lifestyle factors for the elderly, potentially influencing the aging of the immune system and inflammatory cytokines (8). Nikroo et al. (2020) investigated the effects of aerobic, resistance, and combined exercises on the SIRT1 gene expression in male rats. The exercises included eight weeks of treadmill running and stair climbing for five sessions per week. They observed no significant increase in SIRT1 (9). Gaeni et al. (2018) investigated the effect of 12 weeks of high-intensity interval training on the expression of SIRT1, PGC-1α, and ERRα proteins in aged rats. The results showed an increase in SIRT1 expression in the biceps muscle of old rats due to high-intensity interval training (10). Long et al. (2020) reported that eight weeks of treadmill training can activate the NF-κB/SIRT1 signaling pathway by increasing SIRT1 expression, which leads to a reduction in NF-κB expression (11). Conversely, human studies suggest that water-based exercise is a suitable alternative to land-based exercise for the elderly, providing a safe environment for them (12). The unique properties of water, such as buoyancy, adhesion, and hydrostatic pressure, create an ideal environment for enhancing self-confidence and reducing the impact of weight due to gravity, allowing the elderly to engage in exercises or physical activities in a pain-free setting (13).

On the other hand, skeletal muscle is a changeable tissue that adapts according to its activity level through changes in muscle mass, expression of muscle proteins, and changes in contractility and metabolism (14). Both resistance training and aerobic training can increase strength and muscle mass, enhance physical performance, and are effective in preventing and treating sarcopenia in the elderly (15). The present study aimed to determine whether combined exercise in water affects SIRT1 and NF-κB gene expression in fast-twitch and slow-twitch muscles (Tibialis anterior muscle, soleus) of aged male rats.

Methods

The current research is a practical study with a post-test design and a control group. The statistical population consisted of healthy old Wistar rats. A sample of sixteen rats, with an average age of 24 months, was purchased from Kashan University of Medical Sciences and transferred to the Basic Science Laboratory of Hakim Sabzevari University. This research has been registered with the ethics code IR.HSU.AEC.1401.003 and clinical code IRCT20220316054316N1 at Hakim Sabzevari University. The rats were randomly divided into two groups: combined exercise and control, with eight rats in each group. All animals were kept in the same place throughout the study, with an average temperature of 23±3°C, humidity of 50±10%, and a light-dark cycle of 12-12 hours. They had free access to food and water.

The exercises were performed four times per week for ten weeks, alternating between one day of endurance and one day of resistance. The exercises took place in an aquarium measuring 50x50x100 cm, filled with water at the temperature of 30±1°C. The animals were introduced to both endurance and resistance exercises over two weeks with five sessions per week. During the familiarization session for resistance training, exercises were performed in three sets of eight repetitions, with one minute of rest between each set (16,17). These procedures were performed in four sets of ten repetitions, with one minute of rest between each set. Weights were attached to the beginning of the rats' tails with a band. On the first day, the animals swam for five minutes in water at a height equal to 100% of their body length without weights (18). In the following weeks, the training program continued. For endurance training, the container was divided into two parts (25 x 100 cm), allowing each rat to swim individually in a separate lane. During the training period (Four sessions per week), the control group was placed in a container with 5 cm of water for 30 minutes, ensuring they experienced similar physiological stress conditions as the other groups (19).

Forty-eight hours after the last training session, the animals were anesthetized with xylazine and then dissected. In a completely sterilized environment, the anterior tibialis and soleus muscles were extracted from the animals' left legs using a surgical blade. The tissues were immediately frozen in liquid nitrogen and stored in a -80°C freezer for further experiments. The RT-PCR method was used to investigate gene expression changes of SIRT1 and NF-κB proteins. Initially, the samples were incubated for 10 minutes at 95°C. A three-step cycle was then repeated 40 times, consisting of 30 seconds at 95°C, 30 seconds at 58°C to connect the primers, and 30 seconds at 72°C for expansion. Finally, the samples were placed in a thermal cycler for 5 minutes at 75°C to melt. After this step, the PCR product was analyzed using electrophoresis gel to confirm the synthesis of cDNA and the specificity of the desired primers. The relative quantification method was then used to assess the expression levels of the target genes, based on the relative comparison between the target gene and the reference gene in all samples. The beta-actin gene was employed as the reference gene in this research. A specific TaqMan probe was designed for each gene, and the reaction was performed in duplicate. Before performing the main reactions for all samples, the optimal temperature for probe and primer annealing and the optimal probe concentration were determined by performing temperature and concentration gradient experiments. Subsequent reactions for all samples and target genes were performed under these optimal conditions. After the reaction and plotting the proliferation graph, the Ct value for each sample was repeated twice and averaged. Real-time PCR reactions were conducted according to the extension process and temperature protocol of 72°C, with a time of 30 seconds and 40 repetitions for SIRT1 and NF-κB genes. The sequences of the primers and probes for SIRT1 and NF-κB genes are provided in Table 2. All sequences were synthesized by Metabion, Germany. The reactions were performed using the MIC qPCR Cycler. Finally, the data were analyzed with Step One v2.1 software, and the number of target gene copies was determined using the 2-ΔΔCT formula (2 to the negative power of ΔΔCT).

A) ΔCT sample 1 gene 1 = CT sample 1 gene 1 - CT sample 1 Housekeeping

B) ΔCT control 1 gene 1 = CT control 1 gene 1 - CT control 1 Housekeeping

C) ΔΔCT sample 1 gene 1 = ΔCT sample 1 gene 1 - ΔCT control 1 Housekeeping

The normality of data distribution was assessed using the Shapiro-Wilk test. The data were analyzed using a two-way analysis of variance and Benferroni's post hoc test to determine differences between the muscle groups at the $P \leqslant 0.05$ level, using SPSS version 22 software.

Results

The primers for each gene are listed in Table 1. The results of the two-way ANOVA test indicated that after 10 weeks of combined training, there was a significant difference in the SIRT1 gene expression between the training group and the control group, with a significant increase in the combined training group (P=0.001) (Table 2). Benferroni's post hoc test showed no significant difference in the SIRT1 gene expression between the soleus and anterior calf muscle groups within the combined exercise group (P=0.57). Significant differences were observed in the SIRT1 gene expression between the soleus and anterior leg muscles within the exercise group and the control group (P=0.001 and P=0.001, respectively) (Table 3). Additionally, the two-way ANOVA results demonstrated that NF-κB aging indicators were significantly reduced in the training group compared to the control group (P=0.001) (Table 2). Also, Benferroni's post hoc test showed no significant difference in the NF-κB gene expression between the soleus and anterior leg muscles within the combined training group (P=0.99). However, significant differences were observed in the NF-κB gene expression between the soleus and anterior leg muscles within the exercise group and the control group (P=0.001) (Table 3).

Table 1. SIRT1 and NF-κB gene primers in study groups

Genes	Forward	Reverse
NF-Kβ	5'-AGAAGGCTGGAGAAGATGAGG-3'	5'-TTGGTGCCTCGTGTCTTCTGT-3'
SIRT1	5'-ATGACAGAGCATCACACGCAA-3'	5'-CCGCTTTGGTGGTTCTGAAAG-3'

Table 2. Results of the post hoc test for SIRT1 and NF-κB by group

Variables	Mean and Standard Deviation			
	Groups	Average	F	P
SIRT1	Combined exercise	4.35±1.7	1.51	0.001*
	Control	1.5±0.38		
NF-κB	Combined exercise	0.16±0.01	4.07	0.001*
	Control	1.02±0.25		

Table 3. Results of the post hoc test for SIRT1 and NF-κB in soleus and tibialis anterior muscles between groups

Variables		Groups	Mean and Standard Deviation	P
SIRT1 (n/ml)	Combination of soleus muscle	Control + Soleus muscle	1.51±0.8	0.001*
		Control of the anterior tibialis muscle	1.02±0.23	0.001*
		Combination of anterior tibialis muscle	3.82±1.19	0.57
	Combination of anterior tibialis muscle	Control + Soleus muscle	1.08±0.51	0.001*
		Control of the anterior tibialis muscle	1.02±0.23	0.001*
NF-κB(n/μl)	Combination of soleus muscle	Control + Soleus muscle	0.13±0.7	0.001*
		Control of the anterior tibialis muscle	1.30±0.30	0.001*
		Combination of anterior tibialis muscle	0.20±0.11	0.99
	Combination of anterior tibialis muscle	Control + Soleus muscle	1.01±0.20	0.001*
		Control of the anterior tibialis muscle	1.03±0.30	0.001*

Discussion

The results of the present study showed that 10 weeks of combined exercises led to a significant increase in the SIRT1 gene expression and a significant decrease in the NF-κB expression in the elderly rats. However, no significant difference was observed in the gene expression of SIRT1 and NF-κB between the slow-twitch and fast-twitch muscles in the combined exercise group after 10 weeks. In this regard, Pirani et al. (2023) demonstrated that 12 weeks of highly intense intermittent training increased the expression of mitochondrial proteins PGC1α and SIRT1 in the twin muscle of elderly rats (20). Similarly, Huang et al. (2016) examined the effect of 12 weeks of swimming training on the SIRT1 gene expression in the quadriceps and soleus muscles of rats at various ages (3 months, 12 months, and 18 months). The results showed a significant difference in the SIRT1 gene expression among the three age groups, the twin and soleus muscles. After 12 weeks of swimming training, the amounts of SIRT1 protein in the biceps muscle of 18-month-old rats were reduced compared to the baseline. However, it increased in 12-month-old rats. This increase in the SIRT1 gene expression was greater in the soleus muscles of 12-month-old rats than in their twin muscles (21). One reason for the discrepancy in the results between this research and Huang et al.'s research on the effect of exercise training on SIRT1 gene expression changes in elderly rats is the difference in the type and intensity of exercise training. In this research, combined exercises (Resistance-aerobic) were used, which, due to the nature of resistance exercises and muscle involvement in a targeted manner, could be a reason for their greater effect on the SIRT1 gene expression in elderly rats. Moreover, the difference in the type of muscles (Slow or fast contraction) may be another reason for the difference in the results.

Huang et al. investigated the quadriceps and soleus muscle fibers (Slow-twitch fibers). However, we examined soleus (Slow contraction) and anterior leg (Fast contraction) muscles. Therefore, according to the results of this research, swimming exercises can regulate the expression of SIRT1, AMPK, and FOXO3a proteins in leg muscles in elderly rats. In this study, we found that AMPK activation may up-regulate the expression of SIRT1 and PGC-1α in muscles, reducing muscle wasting and improving motor performance in aged mice. SIRT1 plays a vital role in modulating the cytosolic NAD+/NADH ratio in muscle gene expression (22). SIRT1 contributes to skeletal muscle adaptation to endurance exercise, which further modulates SIRT1 downstream targets such as PGC-1α and FOXO1. Consequently, SIRT1 activation is an indirect result of metabolic and transcriptional rearrangements caused by activation (23). Rozestan et al. in the research (2020), the results showed that eight weeks of intermittent training caused a significant increase in the plasma level of SIRT in the heart tissue of diabetic male rats. Therefore, it seems that exercise intensity is an effective factor that has led to an increase in Sirt through stress. Under stressful conditions such as exercise, to maintain the cellular energy load and the ratio of ATP consumption to ATP production, a much larger amount of NADH (resulting from the Krebs cycle and beta oxidation) is oxidized, leading to an increase in NAD+ levels. Therefore the activity of Sirt1, which is dependent on NAD+, also increases. In long-term conditions such as exercise training, the main metabolic adaptations made in skeletal muscle include an increase in the density (Volume and number of mitochondria) and therefore the content of NAD and NADH+ and mitochondrial sensitivity, and consequently, the total mitochondrial content of Sirt3 as well as Sirt1 response to changes in NADH/NAD+ ratio also increases (24).

Chen et al. (2018) showed in a study that swimming training for eight weeks (60 minutes per day) increased the expression of proteins such as SIRT1, PGC-1α, and AMPKα1 in cardiac and tibialis muscles, which are related to energy homeostasis, and inflammatory cytokines related to suppress aging increased in aged mice. Research has shown that during exercise, muscle contraction potentially increases the anti-aging signals associated with SIRT1 and protects against the process of muscle wasting (25). Jenkins et al. (2021) found that eight weeks of combined activity (Aerobic and resistance) did not cause a significant change in the serum SIRT1 level of young women (26). Also, Marton et al. (2015) showed that swimming with an intensity of 70% of VO2max had no significant effect on the SIRT1 gene expression in healthy mice (27). The difference in the number of sessions, the basic level of SIRT1, the type of subject, the nature of the exercise, and the age of the subjects can be reasons for the difference in the results. Therefore, SIRT1 is an important protein during aerobic and resistance exercises that controls metabolic pathways. This function of SIRT1 prevents tissue breakdown, repairs muscles, and increases hypertrophy (28). One of the limitations of this research is that it investigated the effect of ten-week training courses on the expression of genes related to sarcopenia only in elderly subjects and did not compare them with young subjects. Therefore, it is suggested to conduct research aimed at investigating the effect of sports training on gene expression related to sarcopenia in elderly subjects and comparing it with young subjects.

Conclusion

It can be stated that aerobic and resistance exercises can simultaneously affect the NF-κB and SIRT1 signaling pathways of slow-twitch and fast-twitch muscles and be effective in preventing muscle wasting and sarcopenia. Therefore, to manage and improve the aging process, aerobic and resistance exercises are recommended in combination with appropriate intensity and duration. Also, due to having lower risks of falling and injury, water exercises allow the elderly to perform sports movements across a wider range.

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Ethical statement

All practical and research steps were carried out in accordance with the guidelines of the Institute of Health and Nutrition regarding the care and use of laboratory animals and the Ethics Committee of Sabzevar University of Medical Sciences. All ethical activities in research conducted in the years prior to 2021 were legally overseen by Sabzevar University of Medical Sciences.

Conflicts of interest

The authors declare that there is no conflict of interest.

Author contributions

This article is taken from the thesis approved by University of Birjand. The authors gratefully acknowledge the cooperation in this study.

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