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The effect of a selected combination training on the PGC-1α and mTORc1 expression in the quadriceps muscle of aged male rats

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ABSTRACT

Background: Many hormonal and genetic factors are involved in sarcopenia in old age. In the present study, the effect of combined (aerobic and resistance) training was measured on the expression of PGC-1α and mTORc1 genes in the quadriceps muscle of aged rats.

Methods: 16 aged male Wistar rats (22 months old) were randomly assigned to exercise (n=8) and control (n=8) groups. The rats in the exercise group performed 8 weeks of combined (resistance and aerobic) training, and the control group did not participate in the training program. Expression of PGC-1α and mTORc1 genes in quadriceps muscle was measured 48 hours after the last training session. Data were compared between the 2 groups by independent t-test at a significance level of alpha less than 0.5 percent (SPSS 22.0).

Results: Based on analysis data, combined training resulted in significant increase in PGC-1α and mTORc1 genes expression in quadriceps muscle compared with control rats (P=0.001).

Conclusion: Based on the available evidence, combined training may slow down the rate of sarcopenia in old age by increasing PGC-1α /mTORc1 pathway expression. Further studies are needed to understand the underlying mechanisms of this process.

Keywords: Combined training, Sarcopenia, Aged rats, Genes expression, Quadriceps muscle

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Introduction

Today, the world's elderly population is rapidly increasing. By 2050, 1 in 6 people will be over 65 years of age, and the number of people over 80 years of age will triple (1). Aging is associated with a gradual decline in skeletal muscle mass, strength, and function, which may be accelerated in some older adults due to genetic, lifestyle, and other environmental factors (2). Age-related muscle atrophy, or sarcopenia, is associated with adverse outcomes such as increased risk of falls, fractures, decreased function, inability to perform daily tasks, a variety of diseases related to immobility, and mortality (3).

Although there is no definitive cure for sarcopenia, developing strategies to slow the progression of sarcopenia, especially in response to aging, is a debatable challenge. In this context, the Working Group on Sarcopenia in Older

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Adults 2 (EWGSOP-2) has indicated that any strategy to reduce the progression of sarcopenia requires regular exercise (4). Regular exercise, in addition to improving the abnormalities associated with obesity and type 2 diabetes (5), slows the progression of sarcopenia in old age. While aerobic exercise improves skeletal muscle by increasing the number and volume of mitochondria, increasing angiogenesis, and increasing antioxidant capacity (6), resistance training increases skeletal muscle mass by increasing protein synthesis, increasing non-contractile tissue, and reducing protein degradation (7). Thus, the recommendation to perform resistance activities under controlled conditions leads to improved muscle strength and mass, and physical performance in middle-aged and older individuals (8).

It has been mentioned that resistance training is significantly beneficial for preventing sarcopenia by increasing muscle mass and strength. On the other hand, some studies have revealed that aerobic training is a suitable method for preventing age-related muscle mass loss due to the reduction in the expression of catabolic mRNAs (9). Harber et al (2009) showed that 12 weeks of moderate-to-high intensity aerobic training significantly increased muscle size in middle-aged women in addition to improving muscle function and aerobic capacity (10). Based on this evidence, some researchers suggest performing combined training compared to either of these two types of training alone (11). Lundberg et al (2013) showed that combined training produces greater muscle hypertrophy than resistance exercise alone (12). These results effectively demonstrate that aerobic training is a synergistic hypertrophic stimulus for resistance training, without compromising the effects of resistance training.

Adaptations related to combined aerobic and resistance training occur through a complex network of several signaling pathways. One of these factors is PGC-1α, which is a multifunctional transcriptional protein that acts like a switch molecule and regulates genes involved in energy metabolism. This protein plays an important role in maintaining muscle integrity and function during aging by regulating mitochondrial biogenesis and protecting against degenerative processes (13). On the other hand, mTORc1 has also been introduced as another key factor in protein synthesis and inhibiting age-related atrophy. It controls cell growth and protein synthesis and its signaling pathways are affected by factors such as nutrition and exercise (14). On the other hand, it has been stated that compared to resistance training, combined training strongly increases mTORc1 signaling pathways (15). It has also been suggested that activation of the mTOR and PGC-1α signaling pathways is responsible for the physiological changes in muscle in response to aerobic and resistance training (12). Recently, it has been shown that endoplasmic reticulum stress increases mTOR activity, which leads to a decrease in PGC-1α in skeletal muscle (16). It has also been shown that PGC-1α affects mitochondrial function in sarcopenia by affecting the mTOR pathway mediated by sestrin2 (17). In this context, Shirai et al (2021) reported no change in mTORc1 expression following combined exercises in the form of interval training followed by resistance training (18). However, Wang et al (2011) have pointed out that the increase in PGC-1α expression after combined exercises is much greater than when aerobic exercise is performed alone (19).

Despite the aforementioned evidence, no study has been conducted to date to investigate the effect of combined (aerobic-resistance) training on the PGC-1α/mTORc1 signaling pathway in skeletal muscle of elderly populations at risk of sarcopenia. Based on this limitation, the present study aimed to determine the effect of 8 weeks of combined training on PGC-1α and mTORc1 genes expression in the quadriceps muscle of elderly male rats.

Materials and Methods

The present study was an applied and experimental study conducted in 1403. In this study, 16 male Wistar rats, 22 months old, were used. The animals were placed in standard laboratory conditions in terms of light (12-hour light-dark cycle), temperature (22 to 24 degrees Celsius), and humidity (40 to 60 percent). In this study, ethical principles regarding the way animals are handled, including the availability of water and food, and the conditions of their maintenance, were considered. The ethical code IR.IAU.PIAU.REC.1403.002 was obtained from the Islamic Azad University, Parand Branch.

The main criterion for entry into the study is

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old age, or in other words, reaching 22 months of age. After one week of familiarization with the environment, the mice were randomly divided into two groups: a control group and a combined exercise group (aerobic-resistance). Combined exercise included resistance and aerobic exercises, which were performed alternately (resistance exercise first, then aerobic exercise) 5 days a week for 8 weeks according to the following protocol (20, 21) (Table 1).

Resistance training consisted of 5 sessions per week, 3 sets per session, and each set consisted of 4 repetition climbing a special ladder 1 meter high and 26 steps, with a special weight tied to the animals' tails. The rest interval between repetitions was 1 minute and between sets was 3 minutes. For this purpose, the weights were selected according to the weight of the mice, which was weighed at the beginning of each week, according to Table 1, with the aim of applying the principle of overload.

Aerobic training, which included running on a rodent treadmill, also consisted of 8 weeks, with 5 sessions per week. The running speed of the mice was based on a percentage of their maximum oxygen consumption (VO2 max). The method of Hvidal et al (2007) was used to convert the treadmill speed to the maximum oxygen uptake (VO2 max) (21). First, the animals warmed up for 10 minutes at a speed of 10 m/min, and then the progressive exercise test began. Every 2 minutes, the treadmill speed increased by 0.03 m/s (about 1.8 to 2 m/min) until the mice were unable to continue the exercise. 24 hours after the last training session, animals were anesthetized with ketamine (75 mg/kg) and xylazine (10 mg/kg) intraperitoneally. Then, the quadriceps muscle of the animal was extracted.

In order to evaluate gene expression, RNA (Ribonucleic Acid) extraction in muscle tissue was performed according to the Trizol Genex solution protocol, and after its extraction with high concentration and purity, CDNA (Complementary DNA) synthesis steps were performed, then it was used to perform reverse transcription reaction. Measurement of PGC-1α and mTORc1 gene expression levels was performed by quantitative Real Time PCR. In this study, amplification of PGC-1α and mTORc1 genes as well as reference gene (GAPDH) was performed to measure gene expression by Real Time PCR according to the standard method. After the reaction, raw data was extracted from the device in the form of Cycle Threshold (CT) and gene expression levels were calculated using the -ΔΔCt2 method.

Statistical analysis

All statistical analyses were performed through the use of a statistical software package (SPSS, Version 22.0, SPSS Inc., IL, USA). Data were tested for normal distribution by the Kolmogorov-Smirnov test. Comparisons between the means of each group were done using the independent t-test. The differences between the groups were considered to be significant at a p-value of ≤ 0.05.

Results

Body weight changes in the 2 study groups are shown in Table 2. Data represented by Mean and standard deviation. At baseline, no significant difference in body weight was observed between the 2 groups. However, combined training led to a significant decrease in body weight in the exercise group, but body weight in the control group did not change significantly.

Table 1: Distribution of exercise intensity and duration of resistance and aerobic training protocols

Exercise sessions (weekly)		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Resistance training	Intensity (% body weight)	5	10	15	20	30	35	40	45
	Set (Repetition)	3 (4)	3 (4)	3 (4)	3 (4)	3 (4)	3 (4)	3 (4)	3 (4)
Aerobic training	Intensity (%VO2max)	40	45	50	55	60	65	70	75
	Time (min)	10	10	15	20	25	25	30	30

Table 2: Pre and post-training of body weight of 2 groups (Mean ± SD).

Group	**Pre-training**	**Post-training**	**p-value (Paired t test)**
Control	428 ± 26	436 ± 29	*0.448*
Exercise	433 ± 31	401 ± 36	*0.001*
p-value (Independent t test)	*0.411*	*0.009*	-----

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Table 3: Gene's expression after training intervention of exercise and control groups (Mean ± SD).

Variable	Control group	Exercise group	*sig*
mTORc1 expression	1	6.41 ± 0.41	*0.001*
PGC-1α expression	1	2.42 ± 0.36	*0.001*

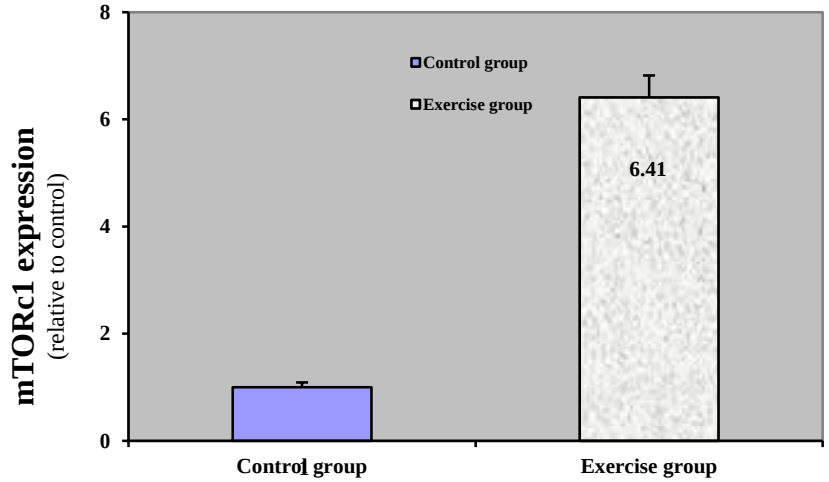

Fig 1: mTORc1 expression in **quadriceps muscle** in exercise rats compares to control group.

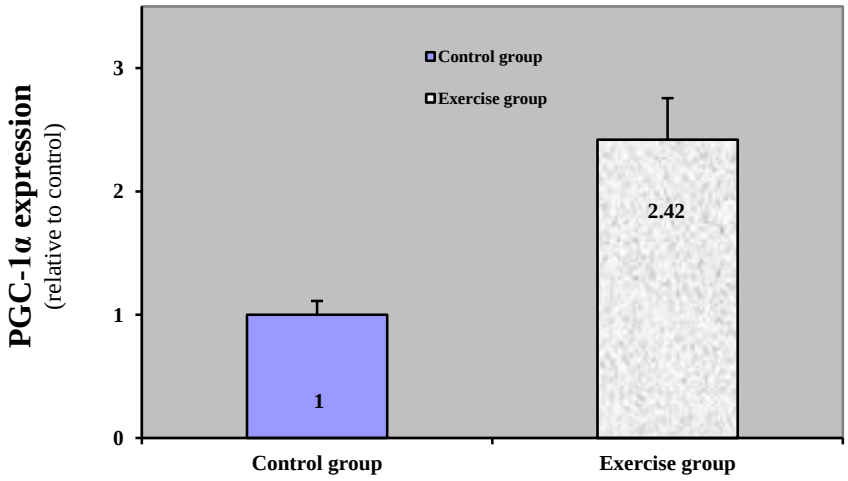

Fig 2: PGC-1α expression in **quadriceps muscle** in exercise rats compares to control group.

The effect of combined training on PGC-1α and mTORc1gene expression in the quadriceps muscle was main aim of current study. Based on independent t test output, mTORc1 gene expression was significantly higher in exercise group than control rats. In other words, 8 weeks combined training in the form of resistance and aerobic exercises resulted in significant increase in mTORc1 expression in the quadriceps muscle compared with control subjects (table 3, Fig 1).

Based on independent t test output, significant differences were also observed between 2 groups with regard to PGC-1α expression. On the other hand, 8 weeks combined training in the form of resistance and aerobic exercises resulted in significant increase in mTORc1 expression in the quadriceps muscle compared with control subjects (table 3, Fig 2).

Discussion

Increased expression of mTORc1 and PGC-1α are the main findings of the present study. In other words, 8 weeks of combined training with 3 sessions per week in the form of resistance and aerobic training led to increased expression of mTORc1 and PGC-1α in the quadriceps muscle of aged male Wistar rats. These findings are reported while mTORc1 is a key regulator of muscle protein synthesis and plays an important role in the development of sarcopenia, loss of

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muscle mass and other age-related muscle disorders. Impaired mTORc1 signaling in the elderly contributes to the progression of sarcopenia. Therefore, increasing activity by expressing it is considered as a potential treatment to combat sarcopenia.

In this context, Shirai et al. also reported in 2021 that combined training in the form of resistance training and HIIT changes the expression of the mTORc1 gene, but the increase in mTORc1 expression occurs when HIIT training is performed first and then resistance training, because in this case, the interfering effects of the two types of training are minimized, and in the group that performed resistance training first and then HIIT training, mTORc1 expression did not change (18). The contradiction in the findings of the aforementioned study can perhaps be attributed to the type of swimming training. It should be noted that even water temperature affects mTORc1 signaling (15). Therefore, performing different types of aerobic training (swimming or running or walking) leads to different results.

Another study found that aerobic exercise after resistance training reduced mTORc1 signaling and reduced protein synthesis compared to resistance training alone (22). Both studies attributed the reduction or inhibition of mTORc1 to the activation of AMPK following aerobic exercise. Other studies have also examined the effect of aerobic exercise on AMPK activity and have shown that although AMPK activity increases during and immediately after exercise, it returns to baseline levels within a few hours of exercise (22). In older men with sarcopenia, aerobic exercise before resistance training has been shown to improve muscle mass and strength (23). On the other hand, Bell et al (2000) have shown that combined exercise can reduce resistance training adaptations such as muscle hypertrophy compared to resistance training alone in adults (24). In another study in rodents, low-frequency electrical stimulation was used as a mimic of aerobic exercise, which resulted in AMPK activation and inhibition of mTORc1 signaling (25). However, a combined exercise session not only did not compromise mTORc1 signaling, but may actually enhance it compared to resistance exercise (12).

On the other hand, another study examined resistance training-induced mTORc1 activation by aerobic exercise and reported no inhibitory effect. In other words, aerobic exercise not only does not reduce growth-related signals via mTORc1 in human skeletal muscle, but mTORc1 activation may inhibit AMPK phosphorylation (26). Cui et al (2019) also reported that high-intensity interval training in the form of treadmill running at 80% of maximal oxygen consumption capacity leads to a decrease in the expression of atherogens downstream of the IGF-1/AKT/FOXO signaling pathway but does not affect mTORc1 expression (27).

Apart from mTORc1, combined training in the present study also led to increased PGC-1α expression in the quadriceps muscle of aged rats. Research has shown the essential role of PGC-1α in mitochondrial biogenesis, slow-to-fast muscle fiber conversion, and resistance to muscle atrophy. High expression of PGC-1α in skeletal muscle of transgenic mice leads to increased mitochondrial biogenesis and oxidative muscle fibers (28). It is believed that combined training has more beneficial effects on general health, mitochondrial biogenesis, and disease prevention than either endurance or resistance training alone. Combined training induces epigenetic changes, including decreased PGC-1α methylation. It should be noted that DNA hypermethylation leads to decreased gene expression, and DNA hypomethylation leads to increased gene expression (29). Epigenetic changes play a major role in exercise-related adaptations. Aerobic exercise induces angiogenesis and mitochondrial biogenesis through AMPK, PGC-1α, and P38 MAPK, and resistance exercise likely stimulates mitochondrial biogenesis through FAK. Aerobic exercise can increase mitochondrial biogenesis and respiration in skeletal muscle, thereby increasing aerobic capacity (30).

Aerobic exercise increases PGC-1α protein expression in skeletal muscle and shows different responses in different muscle types, these different responses may be determined by the two factors AMPK and calcium induced by exercise (31). Wang et al (2011) also reported that although aerobic exercise leads to an increase in PGC-1α gene expression, the effect of combined exercise on PGC-1α expression is much greater than that of aerobic exercise alone. However, Shirvani et al (2020) have pointed out that performing either MICT or HIIT exercise alone leads to a significant increase in PGC-1α

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expression (32). Pirani et al (2022) have also stated that although MICT exercise has beneficial effects on mitochondrial biogenesis, HIIT exercise is more effective than MICT in improving mitochondrial function in aging. Because increasing exercise intensity increases the production of AMP and ADP, which in turn activates AMPK, which is upstream of PGC-1a (33). In addition to AMPK, activation of beta-adrenergic receptors by catecholamines may also stimulate PGC-1α expression by increasing cAMP levels. As shown, 3 weeks of aerobic exercise at 85–90% of maximal oxygen consumption also increased the expression of PGC-1α, TAFM, and AMPK in the soleus muscle of Wistar rats (34). Activation of the mTORc1 and PGC-1α signaling pathways is responsible for specific adaptive responses after aerobic and resistance exercise (33). In conclusion, although the presentation of the findings of this study, which is reported for the first time in this scope, is one of the strengths of the study, the lack of measurement of gene expression or protein expression of other transcription factors effective in sarcopenia in the elderly is a limitation of the study, and further molecular cellular studies are recommended to understand other mechanisms responsible for these changes.

Conclusion

Resistance and interval training are associated with increased expression of mTORc1 and PGC-1α in skeletal muscle in aged rats. Based on the effective distribution of these transcription factors and their associated signaling pathways, it is concluded that combined training in the form of aerobic exercise after resistance training in each training session is associated with improvement of signaling pathways effective in reducing sarcopenia in aged rats. Understanding the main pathways responsible for these changes requires further studies.

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Conflict of interest

The authors declared no conflict of interest.

Authors' contributions

All authors equally contributed to preparing this article.

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