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Simultaneous Effect of Resistance Training and Alpha Lipoic Acid on LC3-1 and P62 Gene Expression of Fatty Liver Diabetic Male Rats

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Abstract

***Background and Objective*:** Autophagy is a genetically and evolutionarily conserved the programmed process that destroys long-lived cellular proteins and organelles. This study aimed to evaluate the effect of eight weeks of strength training with alpha-lipoic acid supplementation on LC3-I and P62 in elderly diabetic rats.

Material and Methods: In this experimental study, 35 old male Wistar rats were randomly divided into 5 groups (healthy control, diabetic, diabetic + strength training, Diabetic + supplement, Diabetic + strength training + supplement). First, the rats became diabetic and had a fatty liver. Strength training program in 10 weeks performed. Alfa-lipoic acid supplement was also injected 3 days a week. At the end of the training period and tissues were removed and the expression of LC3-I and P62 were measured by RT-PCR. For data analysis, a one-way analysis variance test was used for comparison between groups was considered ($P<0.05$).

Results: The result showed mRNA LC3-1 has increased and this change is more in the diabetic group ($P=0.001$) and despite the decrease in P62 gene expression, we did not see a significant difference between the control group and the diabetic in the training group with and without supplementation. However, no significant difference was observed between training methods and supplementation with exercise. Also, resistance training in combination with alpha-lipoic acid supplementation had a significant effect on reducing P62 content between control and experimental groups ($P=0.001$).

Conclusion: Alfa-lipoic acid supplement with anti-oxidant and anti-inflammatory effect along with exercise can play an important role in improving fatty liver in elderly type 2 diabetic rats.

Keywords: Exercise Training, Autophagy [MeSH], Immune System [MeSH], Dietary Supplements[MeSH],

Highlights

Fatty liver may be associated with autophagy. Supplementation with exercise increases the synergistic effects of regulating and improving the disorder. In this experimental study, some indicators of autophagy under the influence of alpha lipoic acid and strength training were investigated. Improvement of inflammatory, oxidative and autophagy factors was a common result of supplementation and exercise.

Introduction

One of the complications of diabetes is a decrease in muscle mass in the lower extremities (1). In old age, the breakdown of muscle protein reduces the volume of muscle mass. Lysosomal autophagy and proteasomal ubiquitin systems are activated during muscle atrophy, which ultimately increases insulin resistance. Autophagy is a self-eating system by which damaged organelles and cellular byproducts are degraded in the lysosome to help maintain cellular homeostasis (2). Autophagy is the major intracellular degradation system and there are three classes: macroautophagy, microautophagy, and chaperone-mediated autophagy (3). Autophagic substrates are nonselective encapsulated and conjugated by the lipid and active form of chain LC3-II and p62 (2). Beclin-1 and LC3-1 are the main regulators of the autophagy pathway. Physical activity and mobility can reduce the process of autophagy. But diabetes increases oxidative stress and physiological changes such as aging, apoptosis, cell growth, and immune response due to autophagy (4). However, a moderate-intensity exercise in male mice improved muscle atrophy and inhibited the autophagy system (1). Also, contradictory findings have been observed acute aerobic exercise is likely to increase the autophagic responses in skeletal muscle (2). Researchers observed that muscle autophagy may be concomitantly altered along with mitochondrial adaptations over the course of chronic muscle activity. Changes in mtor, Beclin 1, LC3-1, and P62 central autophagy genes play a very important role in sarcopenia due to type 2 diabetes in the elderly (5). The first selective adapter for autophagy in mammals is P62, which is also a scaffold and stress-induced protein (6). Multiple P62 domains and their transcription are modulated by oxidative stress (7). With the onset of autophagy, P62 expression decreases (8), but if P62 is overexpressed, the protein accumulates too much and has a protective effect on cell survival. If P62 is removed, the formation of LC3II, exosomes, and autophagosomes is disrupted, which increases cell damage (9). Researchers have shown that low levels of P62 cause ubiquitin-positive masses to form in autophagic mice, so the presence of P62 is essential for the accumulation of these proteins (10). Atg dependent genes encode specific proteins that regulate autophagy. Among the ATGs present, Atg8 or LC3 is a modulatory protein essential for autophagy, biogenesis, and maturation of autophagosomes. When LC3 is degraded in autophagy it is a sign of autophagy substrate. LC3 also regulates the phagocytic process that is LC3-dependent (11). Induction of autophagy increases LC3 levels by a large amount in autophagosomes. Some researchers concluded that continuous and intermittent aerobic exercise combined with atorvastatin supplementation played a significant role in it has decrease in autophagy indicators and can reduce that mechanism in type 2 elderly diabetic rats (12). Also, the effect of 6 weeks of intermittent exercise with selenium nanoparticles on Bcl2 and LC3 gene expression in tumor tissue of female mice showed, LC3 increased in the exercise and the supplement + exercise groups. Consumption

of selenium nanoparticles along with intermittent exercise had a synergistic effect against tumor growth, which is probably due to changes in Bcl2 and LC3 gene expression in tumor tissue (13). Do Keun et al. (2017) studied the effect of exercise on skeletal muscle autophagy in obese rats. The results showed that endurance training had a significant effect on insulin resistance. But no significant difference was observed in Beclin1, P62, Lc3-I, LC3-II as indicators of autophagy in soleus muscle (14). Several studies have shown that methods of training and supplements are effective in the progressive effects of autophagy (15). Also, the basal autophagy flux and autophagy protein expression have been reported to be increased after 4 weeks of voluntary running (16). Some key markers important in examining autophagic flux including the LC3-II/LC3-I ratio, LC3-II, and p62 have been reported to be upregulated (3). Therefore, the aim of this study was to investigate the effects of resistance training with alpha-lipoic acid consumption on LC3-1 and P62 gene expression on soleus muscle tissue of older mice with type 2diabetes and fatty liver.

Materials and Methods

The experiment was performed on male LC3-1 and P62 gene expression mice. The statistical population was 100 old male Wistar rats that had not been studied until the implementation of the training protocol. Rats were purchased from the Pasteur Institute and transferred to the animal room of the university laboratory. Among them, 35 rats were randomly selected as subjects. In this study, rats were kept in separate polycarbonate cages measuring 20×27×47 cm. The ambient temperature was set at 22±1.4°C, the light cycle was set at 12:12 pm and humidity was set at 55% ± 0.6. Rats were fed with foods produced by the Pars-Iran Company Animal Feed Production Center. Also, the water required for each animal was provided in 500 ml bottles for laboratory animals. All stages of the research were carried out in accordance with the ethical principles of working with animals. After a week of familiarity with the laboratory environment, the rats first became diabetic, and then their liver became oily and was randomly divided into 5 groups: healthy control, diabetic, diabetic + resistance training, Diabetic + supplement, Diabetic + resistance training + supplement.

- **Exercise Protocol**

The resistance training protocol included 15 times climbing a special ladder to a height of 1 meter and 46 steps with a distance of 2 cm. A weight was attached to the tails of the rats. In case of refusal to climb, low-watt electric shock was used to stimulate the animal. After 2 weeks of familiarity with animal ladders, the rats performed resistance training for 10 weeks, including 5 sessions per week and each session for 40 minutes (17).

- **Make Diabetes and Fatty Live**

For inducing type 2 diabetes in the study sample, after 12 hours of fasting, a solution of nicotine amide dissolved in normal saline at a dose of 120 mg/kg. After 15 minutes, streptozotocin was used 0.1 M citrate buffer solution was injected intraperitoneally at a dose of 65 mg/kg. By examining blood samples of the eye and fasting glucose above 426 mg/dl, we confirmed that the rats were diabetic (18). To creating fatty liver, the healthy control group was fed a standard diet of rodents and the other groups were fed a high-fat diet for 10 weeks (19). Serum cholesterol concentration was measured as one of the indicators of the fatty liver at the end of the study. Alpha-lipoic acid

supplement, at a dose of 50 mg/kg as a solution of dimethyl sulfoxide, 3 times a week by intraperitoneal injection was given to rats in the training + groups used. Rats in the training group, the healthy control group, and the patient control group received 5% normal saline solution. Because 4 groups are equally affected by the physiological effects of the intraperitoneal injection. In this study, all ethical points of working with animals based on the principles of care and use of laboratory animals approved by the Ethics Committee of the Faculty of Medical Sciences of Islamic Azad University, Varamin Pishva Branch was observed.

- **Tissue Sampling and Laboratory Measurements**

48 hours after the last training session and 10-12 hours of fasting, the subjects underwent intraperitoneal injection of a combination of ketamine and xylazine anesthesia and tissue and blood samples. Gastrocnemius and soleus muscle tissues were isolated and stored at -80°C and blood samples were taken from a vein after surgery, and then sent to the laboratory. Expression of LC3-1 and 62 genes in gastrocnemius and soleus muscle were performed by RT PCR (20).

- **Statistical Analysis**

The normality of the data was assessed using the Shapiro-Wilk test and the homogeneity of variances was assessed by the Leven test. One-way analysis of variance was used to examine the differences between groups. Tukey post hoc analysis for multiple comparisons was used to determine any significant changes between groups ($P < 0.05$, SPSS statistical software, version 21).

Result

- **Effects of Alpha-Lipoic Acid and Resistance Training on Mrna LC3-1**

Mean, standard deviation, and percentage of LC3-1 changes in different research groups were obtained (Table 1). The results showed that the highest mean of LC3-1 in terms of GAPDH changes was observed in the diabetic group (0.05) and the lowest mean was observed in the groups of diabetic + strength training and diabetic + strength training + supplement (0.001). The changes of comparing the expression of the LC3-1 gene in different groups of research with analysis of variance and Tukey post hoc test were calculated (Figure 1). Calculations showed that compared to the healthy control group, a significant increase was observed in the diabetic group (P=0.001). On the other hand, a significant decrease was observed in the groups of diabetic + supplement (P=0.001), diabetic + strength training (P=0.001), diabetic + strength training + supplement (P= 0.001) compared to the diabetic group (P=0.001). Also, data analysis showed that among the diabetic groups, the difference between the strength training and strength +complement groups was similarly significant (P= 0.001). More precisely, compared to the diabetic group, the observed decrease in LC3-1 gene expression was with alpha-lipoic acid supplementation (40%) and strength training (80%).

- **Effects of Alpha-Lipoic Acid and Resistance Training on mRNA P62**

Mean, standard deviation, and percentage of P62 mRNA changes were measured and recorded in different research groups. The results showed that the highest mean was observed in the healthy control group (0.07) and the lowest mean was observed in the

supplement group (0.3). The highest percentage of changes compared to the diabetic group was obtained in the diabetic + supplement group (25%).

The results of one-way analysis of variance on P62 gene expression in elderly diabetic rats with fatty liver were evaluated in different groups. The calculated F value (7.37) and its significance at the level of P=0.001 indicate a significant difference between different groups. Significant comparison of analysis of variance of P62 gene expression in different research groups was calculated by Tukey post hoc test. The results showed that compared to the healthy control group, in all diabetic groups, P62 gene expression levels were significantly reduced (P=0.001). Also, data analysis showed that there was no significant difference between all diabetic groups (Figure 2).

Table 1.Results based on mean ± standard deviation (SD) and the P-values

Group / Variable	Co.	Di.	Di. + Su.	Di. +Tr.	Di.+Su.+ Tr.	P-values.
	Mean ± SD					
LC3I	0.015±0.1	0.055±0.2	0.029±0.002	0.021±0.001	0.019±0.001	0.001*
mRNA P62	0.07±0.009	0.04±0.002	0.04±0.001	0.03±0.02	0.04±0.005	0.001*

*: P≤0.05

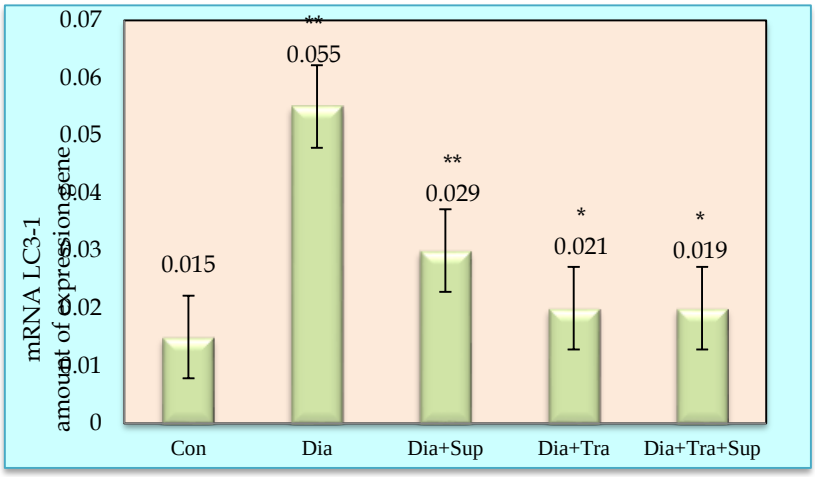

Figure 1. Comparison of mean and significance level of mRNA LC3-1 in 5 research groups
**: Significant difference compared to healthy control group
*: Significant difference compared to the diabetic group

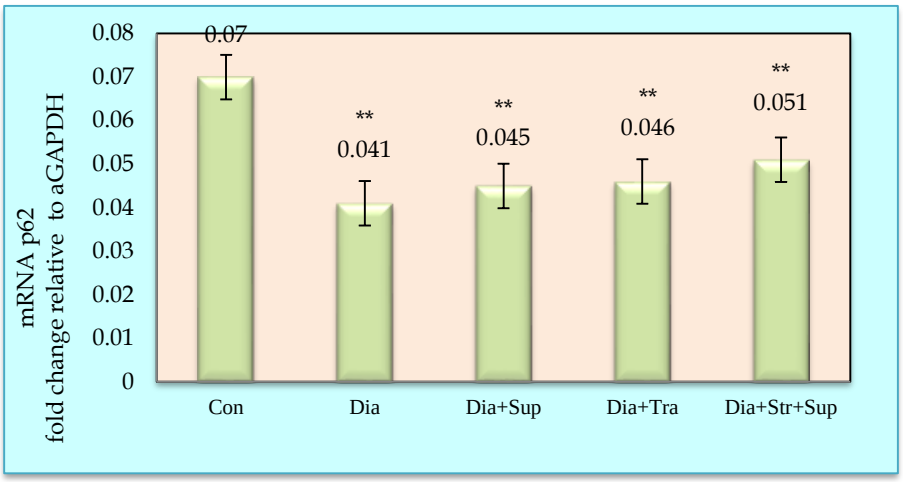

Figure2. Comparison of mean and significance level of mRNA P62 in 5 research groups
**: Significant difference compared to the healthy control group
*: Significant difference compared to the diabetic group

Discussion

- **Response Mrna LC3-I to Alpha-Lipoic Acid and Resistance Training**

The result showed mRNA LC3-1 has increased and this change is more in the diabetic group. Because diabetes increases oxidative stress, aging, apoptosis, cell growth, and immune response to autophagy (4). The increase in LC3-I in other groups was less due to the use of alpha-lipoic acid and strength training protocol. This decrease was due to the effects of adaptation, antioxidants, and strengthening the immune system. Another mechanism is the performance capacity of autophagy regulation, and cellular adaptation which may be independent of the intensity of exercise. In justifying the results, the autophagic response may be affected by the recovery period between training sessions (21). Therefore, exercise as a non-pharmacological intervention can be very effective in the regulation and adaptation of autophagy and there is a synergistic role of exercise and supplementation. The results of their chronic effect showed that exercise increases the protein content of LC3II, which is a sign of increased basal autophagy flow in skeletal muscle (22). Our protocol training reduced the amount of LC3-1 compared to the diabetic. Cho et al. (2017) reported that interval training (10 weeks) did not significantly alter LC3 protein levels and autophagy in the soleus muscle (14) and Majias Pena et al. (2017) also showed that 9 weeks of resistance training did not significantly change the LC3II/LC3I ratio. Because the conversion of LC3-I to LC3-II reduces the rate of autophagy (23). It seems that training and ALA have reduced the number of proteins by creating adaptation in the process of autophagy, the number of free radicals, the accumulation of fatty acids and glucose. In animals, autophagy prevents mitochondria alteration and exacerbated oxidative stress during acute exercise (24). Resistance training and alpha-lipoic acid reduced autophagy and inflammatory markers. Contradictions in the results are due to research projects, animals, physiological and regulatory characteristics of the systems involved (metabolic, immune, muscle).

- **Response Mrna P62 Gene Expression to Alpha-Lipoic Acid and Resistance Training**

The results of this study showed that despite the decrease in P62 gene expression, we did not see a significant difference between the control group and the diabetic in the training group with and without supplementation. Exercise had no effect on changes in P62 gene expression in terms of statistical results. Also, the antioxidant effects of alpha-lipoic acid on oxidative and metabolic reactions were not significant in this section. The amount of P62 in the diabetic group is lower than in the healthy control group. Diabetes appears to impair the activity of this protein. Decreased P62 is associated with autophagy stimulation and accumulates during autophagy. In this study, p62 did not significantly decrease with exercise and supplementation but could be a sign of reduced autophagy. Perhaps if the dose of alpha-lipoic acid was increased or young mice were used, the changes in p62 would be more pronounced. Some studies showed that p62 protein levels were unchanged although the mRNA level of p62 highly upregulated after exercise. If the protein levels were also checked, similar results might be obtained. However, concomitant use of exercise and alpha-lipoic acid resulted in a slight increase in p62 compared to the exercise, diabetic, and supplement groups. It is possible that p62 is a less suitable marker than LC3 I for autophagic flux measurement and p62 may serve other roles besides an autophagic adapter. The results of Majias Pena et al. (2016) did not show a significant change in P62 levels. Also, Young et al. (2018) showed that ALA consumption increased LC3-II protein levels, while P62 protein levels showed a different trend. In addition, skeletal muscle morphological results showed cellular secretion disorders, interstitial edema, physiological disorders, muscle atrophy, and cell muscle hyperplasia (25). But Kwon et al. (2019) measured changes in P62 and other proteins involved in autophagy. Their results were associated with improved autophagic function and antioxidant capacity (26). P62-positive regulating activity or reducing its degradation plays an important role in cancer formation, cancer spread as well as resistance to treatment. It has been shown that in the process of autophagy, the amount of P62 increases, which plays an important role in apoptosis and autophagy (27). In addition, P62 can bind between the nucleus and the cytoplasm and facilitate quality control of nuclear and cytoplasmic proteins (28, 29). Also, P62 involved in regulating the signaling pathways of cell life and death. P62 functions in signal transduction, proliferation, and in response to oxidative stress, and this protein are expressed by induction of autophagy (30). The protein or expression of the p62 gene may be an important marker for autophagy in other cellular processes such as cellular signaling pathways and oxidative stress. Other reasons for the discrepancy may be related to cell lysis buffer (31).

The disadvantages of this study were the use of a small number of samples in groups and the lack of direct involvement of the researcher in the experiments.

The simultaneous effect of exercise (resistance) and supplementation (alpha-lipoic acid) and the selection of expression of two genes of autophagic factors are the strengths of this study.

Research limitations include low sample size, inability to obtain data as a pre-test, and failure to use human samples.

Some research suggestions include the use of other training methods (HIIT, aerobic,

concurrent), other supplements (octopamine, resveratrol), use of other body tissues (liver, brain, blood), and the use of patient samples (with diabetes, liver disorders).

Conclusion

The main findings of this study were that strength exercise and ALA increased the level of mRNA LC3-I and decreased mRNA P62 in rat skeletal muscle. The effect of alpha-lipoic acid and exercise increases antioxidant defense, inhibits oxidative stress damage, reduces autophagy and inflammatory markers. The source of some discrepancies in the results is due to methodological issues, subjects, type, intensity and duration of the training, and other external factors.

Authors' Contribution

Laboratory studies, and tests, study and review, analysis, and interpretation of data: FN., B.Y. and FJ.

Conflict of Interests

No conflict of interest.

Ethical Approval

Code IR. IAU.VARAMIN. REC. 1399. 015.

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