Clinical and Experimental Health Sciences

The Effect Of L-Carnitine And Alpha Lipoic Acid Administration With Exercise In Old Rats On Energy Metabolism Related To Oxidative Stress Parameters

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ABSTRACT

Objective: This study aims to contribute novel insights by investigating the potential positive effects of a combined dietary supplement and exercise program on mitochondrial oxidative stress and energy metabolism in aging. Focusing on the protective impact of Alpha Lipoic Acid (ALA), a potent antioxidant, against exercise-induced mitochondrial oxidative stress in rats, we also assess how L-Carnitine administration affects exercise ability by analyzing resistin and HbA1c levels, indicators linked to insulin resistance and cellular sensitivity.

Method: In this 10-day study, 42 old male Sprague Dawley rats (weighing 400±10 g, aged 15–17 weeks) were divided into six groups (n=7): Control, Exercise, L-Carnitine, Alpha Lipoic Acid (ALA), L-Carnitine+Exercise, ALA+Exercise. Relevant groups received daily oral gavage doses of L – Carnitine (50 mg/ml) and ALA (18 mg/ml). Exercise groups underwent treadmill sessions. On day 10, blood samples were quantitatively analyzed for HbA1c and Resistin levels using a Cusabio ELISA assay kit (China).

Results: ALA supplementation synergistically reduced resistin and HbA1c levels, individually and combined with exercise. Conversely, L-Carnitine supplement, alone or with exercise, increased resistin levels but it caused a decrease in HbA1c levels.

Conclusion: The data indicated a minor, insignificant decrease in resistin levels for the exercise and ALA groups, with a statistically significant difference in HbA1c levels among all groups. Exercise alone positively impacted both HbA1c and resistin levels, suggesting a potential counteraction of age-related oxidative stress and a positive influence on energy metabolism through an appropriate diet and exercise program. Further studies are required to explore specific metabolic pathways and relationships identified in our findings.
Keywords: Aging, exercise, resistin, HbA1c, oxidative stress

1. INTRODUCTION

Aging, a universal stage in living organisms, involves irreversible structural and functional changes at various levels, contributing to degenerative disorders like cancer, obesity, type 2 diabetes, and cardiovascular diseases (1,2). The prevailing oxidative stress hypothesis attributes aging to an imbalance favoring oxidant systems, leading to lipid peroxidation and reactive oxygen species (ROS) release (2). This cellular damage significantly impacts disease pathogenesis. Research on aging primarily concentrates on ROS compounds, emphasizing their crucial role in the aging process (2-4).

Insulin, a crucial hormone in energy metabolism control, undergoes changes in sensitivity and vasodilation in the renal artery during aging, influencing age-related cardiovascular diseases (5,6). Oxidative stress, implicated in damaging lipids, proteins, and DNA, is a key risk factor for age-related cardiovascular and metabolic disorders. Consequently, a positive relationship is suggested between oxidative stress parameters and insulin resistance in old age (6). Mitochondria play a key role in aging, influencing bioenergetics, oxidative stress, cell death regulation, and insulin secretion (4). Research on healthy aging explores therapeutic methods to sustain efficient mitochondrial energy metabolism and reduce oxidative stress. Mitochondrial bioenergetic decline is identified as a crucial factor in age-related diseases, leading to ROS production, mitochondrial DNA damage, pancreatic β-cell dysfunction (7), and diabetes (8) in the physiological aging process.

Exercise involves regular and repetitive physical activity aimed at enhancing the harmony between respiratory and circulatory systems, improving oxygen distribution, metabolic processes, and increasing joint flexibility, muscle strength,

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and endurance (9). Growing evidence from epidemiological and experimental studies suggests that physical activity and exercise can counteract the consequences of aging. Diet and physical factors significantly influence oxidative stress and endothelial function (9-11). Exercise offers various health benefits, especially for the cardiovascular system and muscles, while diet serves as a crucial source of antioxidants. The careful selection of both diet and physical activities plays a key role in preventing cardiovascular and metabolic disorders (10,11).

L-Carnitine is a natural ammonium molecule that can be generated endogenously in all mammalian species in the liver, kidney, and brain from the necessary amino acids lysine and methionine and it is an essential cofactor in the oxidation of fatty acids in the mitochondria. However, since its biosynthesis meets only 25% of the daily requirement, it must be taken into the body through diet or supplementation (12). L-Carnitine, known for enhancing fat burning, improving muscle strength, and endurance, plays a crucial role in treating conditions like diabetes, heart disease, high blood pressure, and a weakened immune system (12,13). Additionally, L-Carnitine functions as an antioxidant, protecting enzymes in the body's antioxidant defense system, such as glutathione peroxidase, superoxide dismutase, and catalase, against advanced peroxidative degradation and age-related diseases (13,14). Numerous studies explore L-Carnitine's impact on exercise capacity and energy balance, enhancing overall physical performance (15). In animal studies, L-Carnitine is suggested to prevent age-related muscle protein breakdown, regulate mitochondrial energy homeostasis, and reduce cellular damage and free radicals (15,16). However, muscle L-Carnitine content declines with age in healthy individuals, hindering its distribution and homeostasis (17,18).

Alpha-lipoic acid (ALA) is a mitochondrial coenzyme, vital for pyruvate dehydrogenase and alpha – ketoglutarate dehydrogenase function (19). As a key cofactor for energy production, ALA is considered a valuable dietary supplement to enhance overall mitochondrial metabolism (19,20). It has demonstrated efficacy in treating disorders related to impaired energy use, including type II diabetes (21), diabetic polyneuropathies, and cardiac ischemia (22) reperfusion injury. The antioxidant properties (23) of (R)-α – lipoic acid contribute to combating increased oxidative stress. Studies also explore the impact of ALA on glucose transport, influencing insulin signaling pathways and blood glucose regulation (24). Given these findings, lipoic acid supplementation is anticipated to offer beneficial effects on energy metabolism, potentially mitigating age-related decline in cardiac metabolism and bolstering antioxidant defense against increased mitochondrial oxidant production with age (25).

The objective of this study was to investigate the protective impact of Alpha-Lipoic Acid, a potent antioxidant, on mitochondrial oxidative stress parameters induced by free radicals resulting from exercise in blood samples obtained from rats under anesthesia. Additionally, we aimed to assess the biochemical enhancement in exercise capacity in animals through the administration of L-Carnitine for energy metabolism. This evaluation involved analyzing resistin and blood glycosylated hemoglobin (HbA1c) levels, known to contribute to insulin resistance by diminishing cellular sensitivity to insulin and impairing glucose uptake. Consequently, the study aimed to explore the interrelation between these variables.

2. METHODS

2.1. Animals and Diet

The number of animals and sample size we used in the study were determined by using similar literature studies based on ethical principles and using the G power analysis method. We obtained 42 male Sprague Dawley rats, aged 15–17 weeks, with a weight of 400 ± 10 g each, from the Düzce University Laboratory Animal Breeding and Experimental Research Center for our research. The rats were housed under a 12-hour light/12-hour dark cycle at a temperature of 22 ± 2°C.

The experimental animals were randomly allocated to cages, with seven animals in each cage. All experimental animals for ten days were fed with standard rat food containing; 88% dry matter, 7% cellulose, 23% protein, 8% raw ash, 2% HCl insoluble ash, 0.9% phosphorus, 1.5% calcium, ,0.7% sodium, 1% salt, 1% lysine, 0.3% methionine. All groups were provided with tap water for drinking, and there were no limitations imposed on the animals' intake of water and feed.

2.2. Ethical Consideration

Our study was approved by Düzce University Animal Experiments Local Ethics Committee (DÜ.ET-2022-02-01).

Table 1. *Content of the Groups and Applications*

Group No	Group Name	Chemicals	Amount	The Delivery Method	Number of Animals
1	Control (K)	-	-	-	7
2	Exercise (E)	-	-	-	7
3	L-Carnitine (L)	L-Carnitine	50 mg/ml	Oral Gavage	7
4	Alpha Lipoic Acid (ALA)	Alpha Lipoic Acid	18 mg/ml	Oral Gavage	7
5	L-Carnitine+Exercise (L+E)	L-Carnitine	50 mg/kg	Oral Gavage	7
6	Alpha Lipoic Acid + Exercise (ALA+E)	Alpha Lipoic Acid	18 mg/ml	Oral Gavage	7

K: Control, E: Exercise, L: L-Carnitine, ALA: Alpha Lipoic Acid

Table 2. *Application Procedure*

Group No	Group Name	Application Procedure
1	Control (K)	• Animals will not be exercised or given any substance. • It will be kept under normal feed-water routine and standard care conditions. • Weight measurement will be made at the beginning and at the end of the experiment.
2	Exercise (E)	• No items will be given. • Weight will be measured at the beginning and at the end. • The following exercise protocol will be applied to the animals on the treadmill without inclination. • Active study (excluding the preparatory period) will last 10 days. • It will be kept under normal feed-water routine and standard care conditions.
3	L-Carnitine (L)	• Animals will not be exercised. • Weight will be measured at the beginning and at the end. • For 10 days, which is the working period, L-Carnitine will be administered at a daily dose of 50 mg/ml in addition to being kept under normal feed-water routine and standard care conditions. • Animals in this group will not be exercised on the treadmill, but the animals will be kept on the treadmill during the exercise to eliminate factors that may occur due to environmental differences.Active study (excluding the preparatory period) will last 10 days.
4	Alpha Lipoic Acid (ALA)	• Animals will not be exercised. • Weight will be measured at the beginning and at the end. • For 10 days, which is the working period, it will be kept under normal feed-water routine and standard care conditions, and in addition to feeding, Alpha Lipoic Acid will be administered at a daily dose of 18 mg/ml. • Animals in this group will not be exercised on the treadmill, but the animals will be kept on the treadmill during the exercise to eliminate factors that may occur due to environmental differences.Active study (excluding the preparatory period) willlast 10 days.
5	L-Carnitine + Exercise (L+E)	• During the study period of 10 days, animals will be given 50 mg/ml L-Carnitine per day by oral gavage 30 minutes before exercise. • The animals will be given the exercise specified on the treadmill, which has no inclination. • Weight will be measured at the beginning and at the end. • Active study (excluding the preparatory period) will last 10 days.
6	Alpha Lipoic Acid + Exercise (ALA+E)	• During the study period of 10 days, animals will be given 18 mg/ml of Alpha Lipoic Acid per day by oral gavage 30 minutes prior to exercise. • The animals will be given the exercise specified on the treadmill, which has no inclination. • Weight will be measured at the beginning and at the end. • Active study (excluding the preparatory period) will last 10 days.

K: Control, E: Exercise, L: L-Carnitine, ALA: Alpha Lipoic Acid

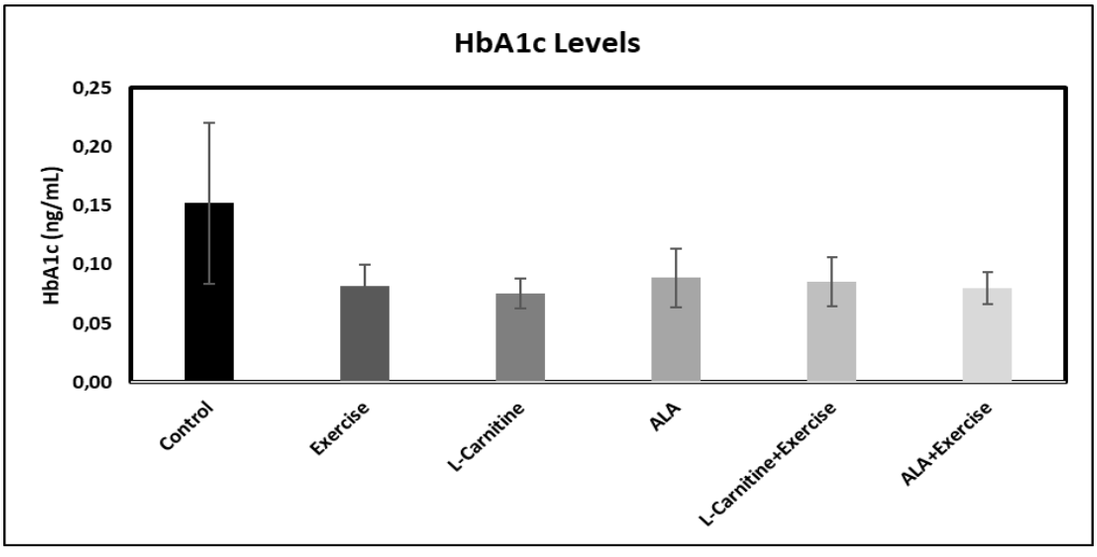

Figure 1. *HbA1c Levels (ng/mL)(ALA: Alpha Lipoic Acid) in groups. Statistical comparisons were run using one-way ANOVA followed by Dunnett's t-test. Statistically significant differences were detected in each group when compared with the control group (p=.001,* p <.05*). The values are represented as mean ± SD.*

Table 3. *Comparison of HbA1c and Resistin levels between groups*

	Control	Exercise	L-Carnitine	ALA	L-Carnitine + Exercise	ALA + Exercise	p*
Resistin	1.1930	1.0529	1.2269	1.1824	1.2490	1.1969	.267
(ng/mL)	±0.2472	±0.1216	±0.0999	±0.1122	±0.1478	±0.1622	
HbA1c	0.1521	0.0819	0.0754	0.0889	0.0856	0.0799	**.001**
(ng/mL)	±0.0686	±0.0177	±0.0124	±0.0250	±0.0207	±0.0135	
p# vs Control		.001	<.001	.004	.002	.001	

*:*One-Way ANOVA, #: Dunnett t test. ALA: Alpha Lipoic Acid*

2.3. Formation of Experimental Groups

In this investigation, six experimental groups (Control, Exercise, L-Carnitine, Alpha Lipoic Acid, L – Carnitine+Exercise, Alpha Lipoic Acid+Exercise) were established, each comprising seven animals. The protocols outlined in Tables 1 and 2 were adhered to for a duration of ten days: At the end of the study, the experimental animals were euthanized under intraperitoneal anesthesia, employing a combination of ketamine (90 mg/kg) and xylazine (10 mg/kg). Cardiac puncture was performed to collect blood samples. Afterwards, the obtained sera were stored at – 80°C.

2.4. Practice of Running Exercise

Features of the Treadmill

All exercise programs applied during our study were carried out using a four-lane experimental animal treadmill branded May TIME 0804 Treadmill Exercise, specially designed for compulsory exercises, fatigue and doping tests.

Preparing Rats for Exercise

All animals were given a trial exercise on the treadmill before the start of the study. Rats that could not run were excluded from the experiment, and the experiment was continued with rats that could run. A 5-day (Monday-Friday) acclimation period was applied for the animals to adapt to the treadmill. Rats were prepared for exercise by running at the lowest speed of the treadmill (2m/min) for 10 minutes.

Exercise Application to Rats

Animals underwent a 10-minute running exercise protocol on a treadmill at a speed of 5 m/min. The exercise protocol was applied for a total of 2 weeks over a 10-day active application period, including the process of acclimating the animals to the treadmill.

Weighing Animals

Weight measurement was made using precision scales at the beginning and end of the experiment. Weighings were made under standard care conditions with normal feeding and water routine.

2.5. Termination of Study

Animals in the groups were sacrificed by taking blood from their hearts by cardiac puncture method under ketamine/xylazine anesthesia after the last administration. After centrifuging the blood samples (15 minutes, 4000 rpm), the serums were extracted and kept at – 80 °C until analysis.

2.6. Measurement of HbA1c and Resistin Levels

After the study, blood samples were utilized to measure HbA1c and Resistin parameters through a quantitative ELISA test kit (Cusabio, China). The spectrophotometric analysis of serum samples was conducted following the protocol provided with a commercially purchased kit, focusing on the specific parameter under investigation. The procedures were carried out in Research Laboratories of Medical Biochemistry Department in Duzce University.

2.7. Statistical Analysis

We conducted statistical analyses using IBM SPSS v.22 software (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). The normality assumption for continuous variables was assessed using the Shapiro-Wilk test, and the homogeneity of variances was examined with the Levene test. The comparison among groups was conducted using the One-Way ANOVA test. Dunnett's t-test was applied to identify significant differences between the experimental groups and the control group, while Fisher's LSD test was employed as a post hoc analysis to assess significant differences among the experimental groups. Mean±standard deviation was used to represent continuous variables. Statistical significance was considered at a level of $p < .05$.

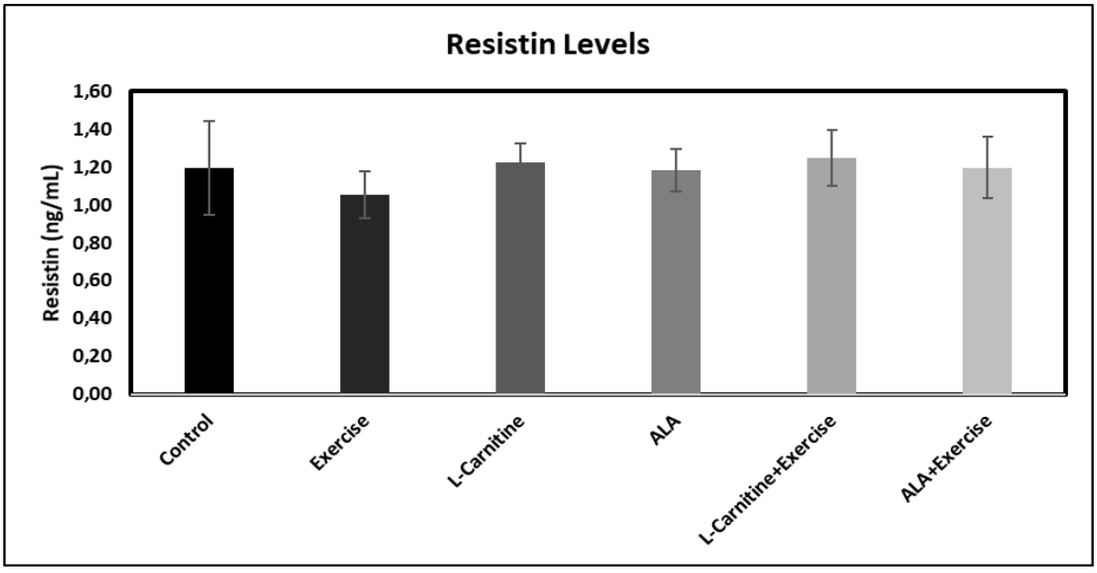

Figure 2. *Resistin Levels (ng/mL)(ALA: Alpha Lipoic Acid) in groups. Statistical comparisons were run using one-way ANOVA followed by Dunnett's t-test. Statistically, no significant difference was detected in any of the groups when compared with the control group (p=.267). The values are represented as mean ± SD.*

3. RESULTS

In all tables and figures, the obtained results are expressed as mean ± standard error.

When the groups' initial and final weights were compared, no significant difference was found. This shows that the 10-day study period is short for us to see the effects of exercise, L-Carnitine and Alpha Lipoic Acid administration on weight changes.

The mean Resistin and HbA1c levels of the experimental groups are presented in Table 3. Analysis revealed that there was no statistically significant difference in resistin levels observed between the groups (p=.267). However, the HbA1c values exhibited significant variability across the groups (p=.001). Post hoc analysis using Dunnett's t-test indicated that the HbA1c level was notably lower in all experimental groups when compared to the control group. Conversely, when the experimental groups were subjected to comparison using Fisher's LSD test, no significant difference was detected among them. Detailed visual representation of the mean HbA1c and resistin levels across the groups can be observed in Figures 1 and 2, respectively.

4. DISCUSSION

In reviewing the existing literature, it is evident that there is a limited number of studies showcasing the potential synergistic effects of applying L-Carnitine and ALA – both known for their individual positive impacts – when combined with exercise in the diet. Our study, designed using an elderly animal model, is anticipated to significantly contribute to the current literature on this subject. We aimed to biochemically evaluate how L-Carnitine administration improves animals' exercise ability by analyzing resistin and glycosylated hemoglobin (HbA1c) levels. The primary objective was to introduce a novel treatment approach, utilizing dietary supplements alongside exercise support, aiming to address the role of mitochondrial oxidative stress and energy metabolism in the aging process. This research endeavors to add valuable insights to the existing body of knowledge in the field.

Resistin is one of the hormones specific to adipose tissue and is a molecule in polypeptide structure. The increase in adipose tissue causes an increase in the level of resistin in parallel. In addition, there is an increase in plasma resistin levels in cases of insulin resistance (26,27). With the advancing age, the body's fat tissue is growing while physical activity is decreasing. In this case, it can be said that the resistin level will result in a high level (28). If there is no change in the fat ratio in the body during exercise activities, it will not be possible for the resistin level to go out of the ordinary (28). As a matter of fact, when the levels of resistin in our study between the groups are examined, it is seen that there is no statistically significant increase or decrease in both the experimental groups and their comparison with the control (Table 3, Figure 2). According to this, it can be concluded that exercise and supplemental alphalipoic acid/carnitine consumption in elderly animals do not cause any negative changes in the fat ratio, and that oxidative stress symptoms do not occur after fat metabolism. The fact that the mentioned supplements do not have negative effects during the application period suggests that the use of the mentioned food supplements in old age will be safe.

L-Carnitine enables cells to break down fat and get energy from stored fat reserves by moving fatty acid chains to the mitochondrial matrix. However, L-Carnitine and its esters help reduce oxidative stress (29). When we interpret it with reference to the fact that resistin is a marker in fat metabolism, the insignificance of the resistin data in our study leads to the conclusion that there is no significant

effect on fat metabolism by administering L-Carnitine to aged rats at the determined dose, duration and exercise application (30). The specific study (30) reported an initial increase in lipid peroxidation and a decrease in antioxidant levels in elderly animals given L-Carnitine supplementation, with subsequent normalization observed after 21 days of administration, attributed to an increase in carnitine status in the body. We referenced this study to highlight existing literature that explores the effects of L-Carnitine on oxidative stress and antioxidant levels in aging animals. The mention of this older study in our publication is intended to contrast with our current research findings, emphasizing potential differences in methodology and study design. This approach aims to contribute to the ongoing discourse in the scientific community and underscore the need for varied research approaches to comprehensively understand the effects of L-Carnitine supplementation in different contexts. Another publication reports that the elderly with reduced muscle carnitine content, decreased lean muscle mass/function, and supplementing with carnitine may have a beneficial effect on mitochondrial dysfunction as well as the benefits of L-Carnitine, especially for the young active population engaged in high-intensity exercise (15). To enhance bioavailability, L-Carnitine supplementation from foods and supplements, supported by exercise, is proposed. Further studies are needed to investigate the current bioavailability of L-Carnitine supplementation.

Hemoglobin is the protein found in red blood cells that carries oxygen. Hemoglobin A1c, on the other hand, is one of the modified forms of hemoglobin formed as a result of the modifications that take place in the posttranslational stages (31). HbA1c, which is formed as a result of glycosylation of blood sugar in plasma by clinging to hemoglobin, is the molecule that plays an active role in the determination of blood sugar (glucose) level (32). When physical activity decreases, HbA1c level increases (33). In this study, a statistically significant reduction in HbA1c levels was observed in both the exercise groups and the supplemented groups (Table 3, Figure 1). These data reveal the conclusion that the blood sugar level in plasma can be reduced with exercise and supplementation in elderly individuals. In addition, based on the decrease in HbA1c level, it is thought that oxidative stress can be reduced to basal levels with supplementary food and exercise, thanks to decreased blood sugar and metabolism. In a meta-analysis of HbA1c levels, data revealed that individuals engaging in both aerobic (18 studies) and heavy exercise (4 studies), as well as a combination of the two (7 studies), experienced a decrease in HbA1c values post-exercise (34). The data we obtained from the running exercise and supplementary applications in old animals are similar to the aforementioned studies.

In addition to being an effective antioxidant, alpha-lipoic acid (ALA) is a natural compound with pro – oxidant properties that occur with excessive consumption (35, 36). The emergence of disruptions in the biological chain with aging results in an increase in oxidative stress (37). There are scientific studies which show that ALA, which is among the antioxidant substances that can be taken into the body, may be effective in reducing this stress. It has been reported that ALA supplementation applied to mice undergoing swimming exercise helps delay oxidative stress resulting from metabolic activity (38).

Kayali et al., when they investigated the effect of ALA applied to aged rats on oxidative stress parameters in post-mitotic brain and muscle tissues, reported that they encountered an increased oxidative stress and that ALA could have a dose-dependent pro-oxidant effect in aged animal tissues (39). The lack of increase in resistin and HbA1c values in our study may indicate that the dose of ALA administered is the dose that will not cause oxidative stress in aged rats.

5. CONCLUSION

In our study investigating the effects of ALA and L-Carnitine supplements on energy metabolism and oxidative stress in elderly rats, we administered these supplements both with and without exercise. Despite not finding significant changes in resistin parameters related to fat energy metabolism, we observed statistical significance in HbA1c data, a critical factor in glucose energy metabolism. The strength of our study lies in its controlled experimental design, utilizing elderly rat models to mimic aspects of aging and incorporating exercise interventions. The inclusion of both supplements and exercise provides a more comprehensive understanding of their potential impacts.

However, it is important to acknowledge the limitations of our study. Firstly, while rat models offer valuable insights, translating these findings directly to humans requires caution. Therefore, future research employing a more detailed experimental design with human subjects is imperative for clinical relevance. Additionally, the 10-day duration of our study may limit the comprehensive assessment of long-term effects. Future investigations with extended durations and more intensive exercise protocols are warranted to validate and elaborate on the observed positive effects.

In conclusion, our results suggest a potential positive impact of ALA and L-Carnitine supplements on glucose energy metabolism in aging. However, further research with human participants and an extended duration is needed for a more robust understanding of the clinical implications and long-term effects of these supplements. Despite these considerations, our study provides valuable insights into the potential benefits of these supplements in mitigating age-related changes in energy metabolism and warrants continued exploration in future research endeavors.

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Acquisition of data for the study:NŞ,AT,AG,TA,KA
Analysis of data for the study:KKK,AT,AG,TA,KA
Interpretation of data for the study:KKK,NŞ,PY,MA
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