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The Effect of Aerobic Exercise and Resveratrol on Endoplasmic Reticulum Stress in Heart Tissue of NAFLD Rats with HFD

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Abstract:

Background: Recent studies have shown that endoplasmic reticulum stress (ERS) plays an important role in the development of non-alcoholic fatty liver disease (NAFLD). The aim of this study was to evaluate the effect of aerobic exercise and resveratrol (RSV) on ER stress in the heart tissue of rats with NAFLD induced by a high-fat diet (HFD).

Methods: In this experimental study, 40 male Wistar rats (weight 159.95 ± 19.70 grams) were assigned to five groups: healthy control (CN), NAFLD, exercise (TNAF), RSV (RSVNAF), and exercise + RSV (TRVNAF). The supplementation groups received 20 mg of RSV (per kg body weight) orally daily during the intervention period. The aerobic exercise program involved running on a treadmill at a speed of 15-20 meters per minute, five days a week for eight weeks.

Results: NAFLD induction resulted in increased GRP78 and CHOP expression (p=0.0001). The expression of GRP78 and CHOP in the TNAF group (p=0.014 and p=0.046, respectively), the RSVNAF group (p=0.015 and p=0.042, respectively), and the TRSVNAF group (p=0.0001) was significantly reduced compared to the NAFLD group. Additionally, the TRSVNAF group showed a significant reduction in GRP78 and CHOP expression compared to the TNAF group (p=0.039 and p=0.038, respectively) and the RSVNAF group (p=0.038 and p=0.041, respectively).

Conclusion: Aerobic exercise and RSV supplementation reduce ER stress by decreasing GRP78 and CHOP expression. However, the combined effect of exercise and RSV was more pronounced.

Keywords: Exercise, Resveratrol, GRP78, CHOP, Non-Alcoholic Fatty Liver Disease, endoplasmic reticulum stress

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Introduction

Non-alcoholic fatty liver disease (NAFLD) is one of the most prevalent metabolic disorders, commonly observed in patients with type 2 diabetes and obesity (1). In addition to hepatic complications, individuals with NAFLD are at increased risk of cardiometabolic disorders such as type 2 diabetes and cardiovascular disease. According to recent data, NAFLD affects approximately 25% of the global adult population and 85–98% of obese individuals worldwide (2). Despite the global concern regarding the health impacts of NAFLD, the underlying mechanisms responsible for its initiation remain poorly understood (3). Recent studies have indicated that endoplasmic reticulum stress (ERS) plays a significant role in the development of NAFLD. The endoplasmic reticulum (ER) is a critical organelle responsible for protein folding, lipid biogenesis, and calcium homeostasis. Stressors that impair ER folding capacity may lead to an accumulation of misfolded proteins and activation of ER stress (4). Although ER stress triggers a compensatory mechanism known as the unfolded protein response (UPR) aimed at restoring ER homeostasis and promoting cell survival, prolonged ER stress—often caused by pathological factors such as lipid accumulation, inflammation, oxidative stress, apoptosis, and autophagy—can exacerbate NAFLD progression (5). Glucose-regulated protein 78 (GRP78) is involved in several key intracellular processes, including the transport, folding, and assembly of newly synthesized proteins, as well as the prevention of protein misfolding and aggregation (6). C/EBP homologous protein (CHOP), a member of the CCAAT/enhancer-binding protein (C/EBP) family, regulates genes involved in cell proliferation, differentiation, gene expression, and energy metabolism. Studies have shown that CHOP-deficient cells exhibit resistance to ER stress-induced apoptosis (6). Therapeutic recommendations for NAFLD primarily include lifestyle and dietary modifications focusing on weight loss and increased physical activity. Accordingly, regular exercise is often advocated as a non-pharmacological strategy to alleviate NAFLD. In NAFLD patients, exercise has been shown to reduce body weight, insulin resistance, and hepatic steatosis (7). Physical activity may also modulate ERS levels across various tissues, thereby improving systemic lipid homeostasis (8). Although compelling evidence supports the lipid-lowering effects of exercise in both humans and animals, some studies have reported inconsistent results regarding its impact on ER stress. For instance, Deldicque et al. (2013) found that endurance training had no significant effect on GRP78 expression (9), and swimming exercise failed to suppress GRP78 elevation in obese aged mice (10). In addition to physical activity, certain natural compounds may influence ER stress. Resveratrol (RSV; 3,5,4'-trihydroxy-trans-stilbene), a polyphenolic compound found in various fruits such as grapes, raspberries, blueberries, and nuts, has demonstrated multiple beneficial effects in cellular, animal, and clinical studies, including anti-tumor, cardioprotective, antioxidant (12), and anti-obesity properties (13). RSV has been shown to be a safe and effective treatment for various human diseases (14, 15). It exerts its effects partly by inhibiting the production of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) through the activation of sirtuin-1 (SIRT1), thereby modulating ER stress (16). Furthermore, previous studies suggest that RSV can affect the ER via the PERK signaling pathway (17). GRP78, activating transcription factor 4 (ATF4), and

CHOP are key ER stress markers downstream of the PERK pathway (18). Six weeks of RSV supplementation has been shown to significantly reduce the expression of phosphorylated PERK (p-PERK), GRP78, ATF4, and CHOP proteins (14). RSV also reduces the expression of GRP78 in macrophages, indirectly decreasing inflammation (19). Given the strong bidirectional relationship between NAFLD and ER stress, identifying effective non-pharmacological interventions is of considerable importance. Considering the roles of exercise and RSV in modulating ER stress markers, the authors of this study hypothesized that a combination of exercise and RSV supplementation would have a greater effect than either intervention alone. Due to the limited and conflicting evidence in this area, the present study aims to investigate the effect of aerobic exercise combined with RSV supplementation on ER stress-related gene expression in the cardiac tissue of NAFLD-induced mice.

Materials and Methods

Animals and Experimental Design

In this experimental study, 40 male Wistar rats (8 weeks old; 159.95 ± 19.70 g) were selected and transferred to the research center. Inclusion criteria included male sex, healthy condition, and no prior drug usage. Exclusion criteria were failure to follow the training protocol, refusal to take the supplement, or injury during the intervention. Animals were kept under standard laboratory conditions and had ad libitum access to food (pellets) and water throughout the study.

After a familiarization period with the treadmill, rats were randomly divided into two groups: healthy control (CN) and NAFLD model. The control group received a standard diet (12% fat, 57% carbohydrates, 28% protein, and 3% other ingredients), while NAFLD was induced in the experimental group using a high-fat diet (22% fat, 50% carbohydrates, 24% protein, and 4% other ingredients) for six weeks \[20]. Subsequently, NAFLD rats were randomly divided into four subgroups (n=8 per group):

1. NAFLD (disease control)
2. NAFLD + exercise (TNAF)
3. NAFLD + resveratrol supplementation (RSVNAF)
4. NAFLD + exercise + resveratrol (TRVNAF)

Only groups assigned to the exercise protocol performed aerobic training for 8 weeks (5 days/week), while others remained sedentary.

Table 1. Composition of Standard and High-Fat Diets

Nutrient	Standard diet	High-Fat Diet
Fat	12	22
Carbohydrate	57	50
Protein	28	24
Others	3	4

Exercise Protocol

Before the main protocol, animals in exercise and exercise-supplement groups underwent a 5-day familiarization period (5 minutes/day at 8–10 m/min, 0% incline). The main aerobic training lasted 8 weeks, starting at 15 m/min for 5 minutes in week 1, with weekly increases of 1–2 m/min in speed and 1–2 minutes in duration. By week 4, intensity reached 20 m/min for 60 minutes and was maintained for the remaining weeks [21]. Warm-up and cool-down sessions of 5 minutes each were included before and after each session.

Table 2. Aerobic Training Protocol

Week	1	2	3	4	5	6	7	8
Duration (min)	5	20	40	60	60	60	60	60
Speed (m/min)	15	17	19	20	20	20	20	20

Resveratrol Administration

Resveratrol (20 mg/kg/day, Sigma-Aldrich) was administered via oral gavage each morning (8:00–10:00 AM) for 8 consecutive weeks. Rats in the control groups received an equal volume of saline solution [22].

Tissue Sampling and Gene Expression Analysis

Forty-eight hours after the last training session and following 12–14 hours of fasting to eliminate acute effects of exercise or supplementation, rats were anesthetized via intraperitoneal injection of ketamine (60 mg/kg) and xylazine (5 mg/kg). Heart tissues were immediately excised, rinsed in saline, weighed, flash-frozen in liquid nitrogen, and stored at −80°C until analysis.

Primer Design and RNA Extraction

Primers were designed as shown in Table 3. Total RNA was extracted from cardiac tissues and converted into cDNA. Real-time PCR was then conducted to assess the expression levels of target genes.

Table 3. Primer Sequences for RT-PCR

Genes	Forward primers	Reverse primers
GRP78	5′- CTGAGGCGTATTTGGGAAAG-3′	5′- TCATGACATTCAGTCCAGCAA-3′
CHOP	5′- CTTGAGCCTAACACGTCGATT-3′	5′- TGCACTTCCTTCTGGAACACT-3′
β-actin	5′- GTCACCCACACTGT GCCCATCT-3′	5′-ACAGAGTACTTGCGCTCAGGAG-3′

Real-Time PCR Procedure

Approximately 20 mg of tissue was homogenized, and total RNA was extracted using TRIzol reagent. RNA was then reverse-transcribed into cDNA, and real-time PCR was performed using SYBR Green master mix (Thermo Scientific, USA) and the designed primers. The thermal cycling conditions were as follows:
Initial denaturation: 95°C for 10 minutes
40 cycles of:

Denaturation: 95°C for 20 seconds
Annealing: 60°C for 30 seconds
Extension: 72°C for 50 seconds
Gene expression was quantified using the comparative Ct (ΔCt) method. The difference between the Ct of the target and reference gene (β-actin) was calculated (ΔCt = Ct_target − Ct_control), and relative expression was analyzed using the 2^-ΔCt formula.

Statistical Analysis

Normality of data distribution was assessed using the Shapiro-Wilk test. One-way ANOVA followed by Tukey's post-hoc test was used for comparing mean differences among groups. The significance level was set at *p* ≤ 0.05. All statistical analyses were conducted using SPSS version 26.

Results

The mean body weights of the rats before and after NAFLD induction, as well as at the end of the protocol, are presented in Table 4.

Table 4. Mean body weights (g) of rats in different groups before and after NAFLD induction and at the end of the protocol

Group	Before NAFLD Induction	After NAFLD Induction	End of Protocol
CN (n=8)	158.88 ± 19.49	222.63 ± 15.71	275.50 ± 13.43
NAFLD (n=8)	153.63 ± 15.87	154.50 ± 15.09	314.87 ± 12.24
TNAF (n=8)	158.13 ± 10.23	262.88 ± 22.38	284.13 ± 20.32
RSVNAF (n=8)	168.50 ± 41.17	268.75 ± 20.73	299.25 ± 18.66
TRSVNAF (n=8)	160.63 ± 10.15	251.13 ± 18.20	268.38 ± 11.41

Analysis of GRP78 gene expression in cardiac tissue revealed a significant difference among groups (F=14.186, p=0.0001) (Figure 1). Post hoc analysis indicated a significant increase in GRP78 expression in the NAFLD (p=0.0001), TNAF (p=0.032), and RSVNAF (p=0.031) groups compared to the CN group. Furthermore, GRP78 expression significantly decreased in the TNAF (p=0.014), RSVNAF (p=0.015), and TRSVNAF (p=0.0001) groups compared to NAFLD. Additionally, GRP78 levels were significantly lower in the TRSVNAF group compared to TNAF (p=0.039) and RSVNAF (p=0.038).

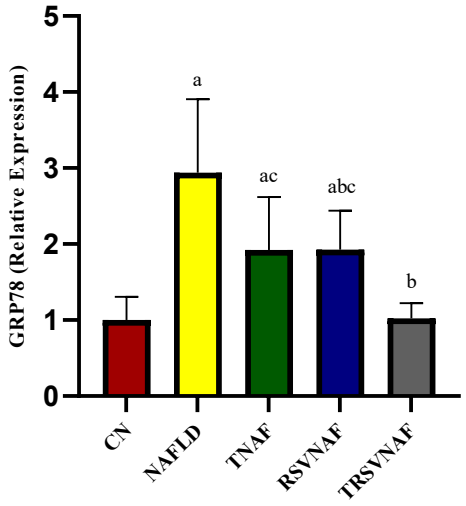

Figure 1. GRP78 gene expression changes across experimental groups.
a: significant difference from CN, b: from NAFLD, c: from TRSVNAF Abbreviations: CN: Control Normal Diet, NAFLD: Non-Alcoholic Fatty Liver Disease, TNAF: NAFLD+Training, RSVNAF: NAFLD+Resveratrol, TRSVNAF: NAFLD+Training+ Resveratrol.

Similarly, analysis of CHOP gene expression in cardiac tissue demonstrated a significant difference among groups (F=12.172, p=0.0001) (Figure 2). Post hoc comparisons showed a significant increase in CHOP expression in the NAFLD (p=0.0001), TNAF (p=0.040), and RSVNAF (p=0.044) groups compared to the CN group. Significant reductions were observed in TNAF (p=0.046), RSVNAF (p=0.042), and TRSVNAF (p=0.0001) groups compared to NAFLD. Moreover, the TRSVNAF group showed significantly lower CHOP expression compared to both TNAF (p=0.038) and RSVNAF (p=0.041).

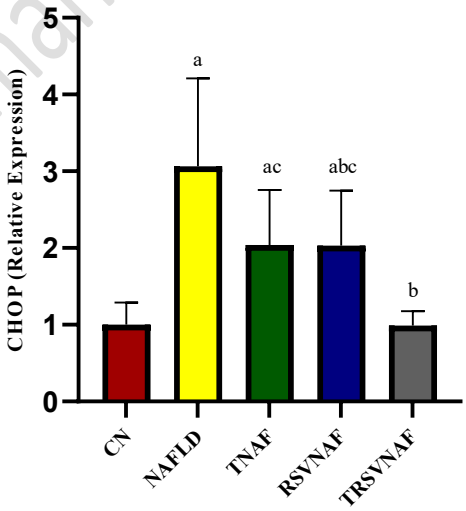

Figure 2. CHOP gene expression changes across experimental groups.
a: significant difference from CN, b: from NAFLD, c: from TRSVNAF
Abbreviations: CN: Control Normal Diet, NAFLD: Non-Alcoholic Fatty Liver Disease, TNAF: NAFLD+Training, RSVNAF: NAFLD+Resveratrol, TRSVNAF: NAFLD+Training+ Resveratrol.

Discussion

The results of the present study indicated that NAFLD induction led to an increase in the expression of GRP78 and CHOP in liver tissue. Consistent with our findings, Lei et al. (2021) showed that after inducing NAFLD using a high-fat diet (HFD), the expression of GRP78, CHOP, and Atf4 (Activating Transcription Factor 4) in the liver of mice was increased (23). Additionally, Mansour et al. (2022) demonstrated that HFD-induced NAFLD in rats was associated with an increase in CHOP expression and ER stress (ERS) (24). It has been reported that HFD induces NAFLD through increased insulin resistance, leading to impaired insulin-mediated glucose reduction, elevated serum triglyceride (TG) and total cholesterol (TC) levels, and increased body and liver weight. These changes are associated with liver damage and hepatic steatosis (25). GRP78, as a major ER marker and the most abundant glycoprotein in the ER, serves as a biological marker of ERS. It appears that ERS can lead to increased TC synthesis in hepatocytes, resulting in fat deposition and the exacerbation of NAFLD. The increased expression of GRP78 and CHOP following NAFLD has also been confirmed in other studies (26).

The results of the present study showed that exercise training led to a reduction in the expression of GRP78 and CHOP. The pathophysiology of NAFLD is believed to be related to ER dysfunction (5). Li et al. (2022) demonstrated that HFD-induced NAFLD, which was associated with lipid dysregulation and liver dysfunction, led to an increase in the expression of GRP78 and ATF6. However, exercise reversed this process, improving ERS (27). Tan et al. (2018) also showed that six weeks of physical exercise reduced the expression of GRP78 in a NAFLD mouse model (28). In another study by Li et al. (2022), it was observed that physical activity reversed the increased expression of CHOP in HFD-induced NAFLD mice (29). Păunescu et al. (2020) showed that treadmill aerobic exercise reduced the expression of GRP78, CHOP, XBP1, and caspase-3 (30). However, several studies have indicated that exercise has no effect on ERS markers (9, 10). According to previous reports, GRP78 expression is influenced by exercise intensity. Therefore, the regulation of ERS could depend on the type, intensity, and duration of physical activity. ERS markers may increase or decrease after exercise, but the beneficial effects of physical activity on NAFLD are generally consistent. Exercise positively affects NAFLD by reducing liver fat content. Physical activity can prevent the accumulation of misfolded proteins, reduce oxidative damage, increase heat shock proteins, and improve exercise tolerance. The metabolic stress induced by exercise can activate the UPR and mediate the adaptive response to exercise. However, the biological responses vary based on intensity and duration, inducing different degrees of ERS (31). Moreover, it seems that physical exercise improves ER pressure through the AMPK/SREBP-1c/mTOR signaling pathway. Li et al. (2014) demonstrated that exercise reduces fat accumulation caused by SREBP-1c in the liver via the AMPK pathway, inhibiting mTOR and improving ERS (32). Overall, physical activity regulates ERS by influencing the XBP1 and hepatic SREBPs signaling pathways, thereby reducing fat accumulation in the liver and alleviating NAFLD.

In addition to exercise, diet also affects ERS in the liver. In recent years, most research has focused on natural products or plant chemicals with lipid-modulating, antioxidant, and anti-inflammatory effects. One of the results of the present study was the reduction of serum GRP78

and CHOP levels following RSV (Resveratrol) consumption. It has been shown that a high-fat diet is associated with increased ERS markers such as GRP78 and CHOP (33), and RSV consumption reverses this process. Moreover, RSV has been reported to protect against hepatic steatosis and ERS in high-fat diet-fed mice (34). Yuan et al. (2018) also found that RSV reduced renal GRP78 expression in diabetic mice (14). The reduction of ERS in NAFLD following RSV consumption suppresses inflammation by modulating TNF-α and NF-κB expression, thereby potentially inducing anti-obesity effects. Additionally, RSV has been shown to reduce GRP78 expression in macrophages, indirectly mitigating inflammation (35). Yan et al. (2018) demonstrated that RSV reduced ERS by decreasing GRP78, XBP1, and apoptosis markers (CHOP and caspase-12), while increasing autophagy markers (LC3II and beclin-1) and antioxidant enzyme activity (CAT and SOD) in neuronal cells (36). Ardid-Ruiz et al. (2018) showed that RSV protects against ERS by influencing leptin-SIRT1 signaling. Their study indicated that the reduced expression of sXBP1 following RSV consumption decreased ERS in adipose tissue. Furthermore, RSV-induced overexpression of SIRT1 was one of the mechanisms by which leptin signaling was enhanced, thereby improving ERS (37).

Another finding of the present study was the reduction of serum GRP78 and CHOP levels in the combined group compared to other groups. In line with this, Bal et al. (2022) showed that the combination of regular exercise and RSV modulated cellular responses, including oxidative stress and ERS (38). Zhang et al. (2021) reported that eight weeks of aerobic exercise combined with curcumin reduced ERS by inhibiting the IRE1α-XBP1 pathway, affecting GRP78 and CHOP expression (39). It seems that ROS production induced by NAFLD plays a significant role in ERS, and both exercise and RSV have antioxidant effects, which may contribute to improving ERS markers such as GRP78 and CHOP. In the present study, the simultaneous effect of exercise and RSV was greater than either factor alone, indicating a synergistic effect on GRP78 and CHOP. One limitation of the current study was the lack of analysis of oxidative stress and inflammatory markers, as well as other variables influencing ER, due to cost constraints. These factors could have provided a better understanding of the effects of exercise and RSV.

Conclusion

In the present study, both exercise and RSV significantly reduced serum levels of GRP78 and CHOP in NAFLD. One of the possible mechanisms underlying the beneficial effects of exercise and RSV on ERS may involve modulation of these markers. The combined effect of exercise and RSV was more pronounced than either intervention alone. Therefore, it seems that at least part of the beneficial effects of the non-pharmacological interventions, exercise and RSV, on improving metabolism, oxidative stress, and ERS in NAFLD are mediated by the reduction of GRP78 and CHOP. It is recommended to use the combination of these two interventions in NAFLD to improve ERS.

Compliance with ethical guidelines

This study was approved by the Research Ethics Committee of the Islamic Azad University, Ayatollah Amoli Branch, with the code IR.IAU.AMOL.REC.1401.116.

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Conflicts of interest

The authors declare that they have no competing interests.

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Authors' contributions

Concept/Design- A. Abdi. Acquisition of Data-S. Rezvani. Data Analysis/Interpretation- A. Abdi. Drafting of the manuscript- A. AbdI/S. Rezvani. All authors approved the final version of the manuscript.

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