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The Impact of Aerobic Exercise Combined with Lactobacillus Supplementation on the Expression of Adiponectin and Appl1 Genes in the Liver Tissue of Wistar Rats with Fatty Liver Disease

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A B S T R A C T

Objective: The present study aimed to investigate the effects of aerobic exercise combined with Lactobacillus supplementation on the expression of adiponectin and APPL1 genes in the liver tissue of rats induced with fatty liver.

Materials and Methods: A total of 32 rats with an average weight of 220±20 grams were divided into 4 groups: 1. FLCG (Fatty liver control group), 2. FLLSG(Fatty liver with Lactobacillus supplementation group), 3. FLAEG: (Fatty liver with aerobic exercise group), 4. FLAELS(Fatty liver with combined aerobic exercise and Lactobacillus supplementation group).The first group was fed a standard rodent diet, while the fatty liver groups were converted into a model group by receiving tetracycline via gavage. In the exercise and exercise ± supplementation groups, aerobic training was conducted on a treadmill for 6 weeks, 5 days a week. The supplementation groups received 109 CFU/ml of Lactobacillus rhamnosus GG daily via gavage for 5 weeks. Surgery and liver biopsy were performed at the end of the study. The expression levels of adiponectin and APPL1 genes in liver tissue were measured using Real-Time PCR technique. All data from this study were analyzed using SPSS version 24. Two-way ANOVA and Tukey's post-hoc test were used for intergroup comparisons, with a significance level set at $p<0.05$.

Findings: The findings regarding adiponectin gene expression indicated no significant difference between the control group and the supplementation group ($p=0.401$). However, both aerobic exercise and aerobic exercise with supplementation groups showed significant differences compared to the control group ($p=0.001$). Thus, aerobic exercise combined with Lactobacillus supplementation significantly affects adiponectin gene expression in the liver tissue of rats with induced fatty liver. Similarly, results for APPL1 gene expression showed no significant difference between the control and

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supplementation groups (p=0.200), but both aerobic exercise and aerobic exercise-supplementation groups exhibited significant differences compared to the control group (p=0.001). Therefore, aerobic exercise combined with Lactobacillus supplementation significantly impacts APPL1 gene expression in the liver tissue of rats with induced fatty liver.

Conclusion: The results of this study indicate the effective role of aerobic exercise and Lactobacillus consumption on the expression of adiponectin and APPL1 genes in liver tissue in laboratory samples of fatty liver disease. If the exercise regimen is sufficiently intense and prolonged, it can play a major role in treating fatty liver.

Keywords: *Aerobic exercise, Lactobacillus, Adiponectin, APPL1, Fatty liver*.

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is a significant global health concern characterized by excessive fat accumulation in the liver, affecting individuals who consume little or no alcohol. This condition encompasses a spectrum of liver pathologies, ranging from simple hepatic steatosis to non-alcoholic steatohepatitis (NASH), fibrosis, and cirrhosis. NAFLD is closely associated with metabolic disorders such as obesity, type 2 diabetes, and dyslipidemia, contributing to increased morbidity and mortality due to complications like cardiovascular disease and liver cancer (1, 2). The prevalence of NAFLD has risen dramatically in recent years, paralleling the global obesity epidemic, with estimates suggesting that approximately 25% of the adult population in Western countries is affected by this condition (3). The relationship between fatty liver disease and gene expression in the liver is crucial for understanding its pathophysiology. Various studies have identified distinct hepatic gene-expression patterns associated with different stages of NAFLD. For instance, research has shown that genes involved in lipid metabolism, inflammation, and fibrosis are differentially expressed as the disease progresses from simple steatosis to more severe forms like NASH (4). Specifically, inflammatory markers and profibrotic genes are upregulated in advanced stages of the disease, indicating a complex interplay between metabolic dysregulation and hepatic gene expression (5). Understanding these gene expression changes is vital for developing targeted therapeutic strategies for NAFLD (6). Adiponectin, an adipocyte-derived hormone, plays a critical role in regulating glucose levels and fatty acid breakdown. It exhibits anti-inflammatory properties and enhances insulin sensitivity, making it a key factor in metabolic health (7). Adiponectin levels are inversely correlated with body fat percentage; thus, individuals with obesity often present lower adiponectin levels (8). Its protective effects against hepatic steatosis have made adiponectin a focus of research in the context of NAFLD (9). Increased adiponectin levels are associated with improved metabolic profiles and reduced liver fat content (10). APPL1 (adaptor protein containing PH domain, PTB domain, and leucine zipper motif 1) is another critical protein involved in insulin signaling pathways. It serves as a scaffold for various signaling molecules and modulates adiponectin receptor signaling (11). Dysregulation of APPL1 has been linked to insulin resistance and fatty liver disease (12). Studies indicate that APPL1 expression is decreased in states of metabolic dysfunction, suggesting its potential role as a therapeutic target for managing NAFLD (13). Research has demonstrated that both adiponectin and APPL1 are significantly affected by the presence of fatty liver disease. Lower adiponectin levels correlate with increased hepatic fat accumulation and inflammation (14), while APPL1 expression decreases with worsening insulin resistance observed in NAFLD patients (15).

Interventions aimed at increasing adiponectin levels or enhancing APPL1 signaling have shown promise in improving metabolic outcomes and reducing liver fat content (16). Management strategies for fatty liver disease emphasize lifestyle modifications, particularly through diet and exercise. Regular physical activity has been shown to improve insulin sensitivity, reduce visceral fat, and promote weight loss—all critical factors in reversing or preventing the progression of NAFLD (17). Exercise can lead to significant improvements in liver function tests and histological features of liver tissue affected by fatty liver disease (18). Aerobic exercise specifically has emerged as an effective intervention for managing fatty liver due to its ability to enhance cardiovascular fitness while promoting fat oxidation. Studies have shown that aerobic training can lead to reductions in liver fat content, improvements in metabolic parameters, and increased adiponectin levels among

individuals with NAFLD (19). These benefits underscore the importance of incorporating aerobic exercise into treatment plans for patients at risk of or suffering from fatty liver disease (20). The relationship between aerobic training and the expression of adiponectin and APPL1 further supports exercise as a therapeutic modality for NAFLD. Increased physical activity has been associated with elevated adiponectin levels, which may contribute to improved insulin sensitivity and reduced hepatic steatosis (21). Additionally, exercise may enhance APPL1 signaling pathways, thereby promoting better metabolic outcomes in individuals with fatty liver disease (22). Incorporating food supplements alongside exercise can complement lifestyle interventions for managing fatty liver disease. Nutritional supplements may provide additional support for metabolic health by enhancing the effects of physical activity on liver function. Research indicates that certain dietary components can modulate gene expression related to lipid metabolism and inflammation, thus playing a supportive role in the management of NAFLD (23). Lactobacillus supplementation represents one such dietary intervention gaining attention for its potential benefits on gut microbiota composition and metabolic health. Probiotics like Lactobacillus have been shown to improve gut barrier function, reduce systemic inflammation, and influence lipid metabolism favorably (24). These effects may contribute positively to managing conditions like NAFLD by addressing both metabolic dysregulation and gut health simultaneously (25). Investigations into the effects of Lactobacillus supplementation on fatty liver have yielded promising results. Studies suggest that probiotics can help lower hepatic fat accumulation while increasing adiponectin levels, thereby mitigating some adverse effects associated with fatty liver disease (26). Furthermore, Lactobacillus may interact synergistically with exercise to enhance overall metabolic health outcomes (27).

Addressing fatty liver through non-drug approaches such as lifestyle modifications—including dietary supplements—offers a promising avenue for management without reliance on pharmacological treatments. This holistic approach not only targets weight reduction but also aims at improving hepatic function through natural means. The synergy between dietary supplements like Lactobacillus and exercise raises intriguing questions about their combined effects on metabolic health. Understanding how these interventions work together could provide insights into optimizing treatment strategies for individuals with fatty liver disease while minimizing reliance on medications. In summary, this study aims to explore the combined effects of aerobic exercise and Lactobacillus supplementation on adiponectin and APPL1 gene expression in Wistar rats with fatty liver. By investigating these interactions, we hope to elucidate potential mechanisms underlying effective non-pharmacological strategies for managing fatty liver disease.

2. Methods and Materials

2.1 Study Design

This experimental study was conducted on male Wistar rats to investigate the effects of aerobic exercise and Lactobacillus supplementation on liver tissue gene expression. Forty 8-week-old male Wistar rats (initial weight 220±20g) were obtained from the Razi Serum Institute's laboratory animal breeding center.

2.2 Housing Conditions

The animals were housed in transparent polycarbonate cages (15×15×30 cm) under controlled conditions: temperature (22±3°C), relative humidity (30-60%), and 12:12 hour light-dark cycle. Rats had free access to water (10-12 mL/100g body weight daily) through specialized 500-mL laboratory animal bottles. Following a two-week acclimatization period, the experimental procedures commenced.

2.3 Experimental Groups

The rats were randomly allocated into five groups (n=8 per group): 1. Fatty liver control group, 2. Fatty liver with Lactobacillus supplementation group, 3. Fatty liver with aerobic exercise group, 4. Fatty liver with combined aerobic exercise and Lactobacillus supplementation group

2.4 Fatty Liver Model Induction

Oral tetracycline (140 mg/kg body weight, dissolved in 2 mL water) was administered to rats via gavage for 7 days. Confirmation of fatty liver (steatosis) was achieved through liver enzyme measurements and hematoxylin-eosin staining (28).

2.5 Bacterial Culture and Probiotic Administration

Lactobacillus rhamnosus GG (PTCC1637) was obtained in lyophilized form from the Iranian Research Organization for Science and Technology (Tehran, Iran). The bacteria were cultured in MRS medium (Zisti Gouya, Tehran, Iran)

enriched with L-cysteine HCL and incubated at 37°C for 24 hours. The probiotic intervention groups received daily doses of L. rhamnosus GG (109 CFU/mL) via gavage for 5 weeks, 5 days per week (29).

2.6 Aerobic Exercise Protocol

The aerobic exercise protocol consisted of six weeks of treadmill running, initiated after a one-week familiarization period. The familiarization phase involved running at 5-10 m/min for 20-30 minutes daily over 5 days. The main exercise program began at 14 m/min during the first two weeks, progressively increasing to 18 m/min in the final two weeks. To control for treadmill-induced stress, the control and Lactobacillus groups maintained regular cage activity.

Exercise training included:

- Familiarization: 5-10 m/min for 30 minutes
- Main protocol: 30 minutes at 18 m/min, 5 days/week for 6 weeks
- Each session included 5-minute warm-up and cool-down periods at 5 m/min
- Motivation was provided through gentle tail touching; no electric shock was used

The VO2max index was calculated using the formula:

VO2max Index = [Maximum speed (m/min)] × [Grade (%) × 100] × [BW (kg)]

where a 0-degree grade equals 1 in the equation.

2.7 Tissue Sampling

After the experimental period, following 12-14 hours of fasting and 48 hours after the final exercise session, animals were euthanized using intraperitoneal injection of ketamine and xylazine. Liver samples were extracted and homogenized in phosphate-buffered saline (pH=7) at 4°C, then centrifuged at 12,000 rpm for 15 minutes at 4°C. The resulting samples were immediately stored at -80°C for subsequent analyses.

2.8 RNA Extraction

Tissue samples were processed on RNase-free slides and transferred to RNase-free microtubes. The homogenization process involved: 1. Addition of 700 µL Trizol solution 2. Addition of 200 µL chloroform for phase separation 3. Centrifugation at 12,000 rpm for 10 minutes 4. Collection of the clear RNA-containing supernatant 5. Addition of equal volume isopropanol 6. Overnight incubation at -20°C 7. Centrifugation at 12,000 rpm for 10 minutes 8. Washing with 1000 µL 75% ethanol 9. Final centrifugation at 7,000 rpm for 10 minutes 10. Resuspension in 30-50 µL distilled water

2.9 RNA Quality and Quantity Assessment

RNA quality and quantity were evaluated using nanodrop spectrophotometry and agarose gel electrophoresis. The nanodrop automatically calculated RNA concentration using optical density at 260 nm wavelength. Multiple controls were employed throughout the experiment to minimize false positive and negative results, given RT-PCR's high sensitivity and RNA's inherent instability.

2.10 Real Time PCR primers

To study the expression of target genes in rats, specific primers for the cDNA sequence of each gene were designed using Oligo Analyzer and Primer3 Plus software. Their analysis and optimization characteristics were verified using BLAST. In Real-time PCR technique, to analyze samples, the cycle number at which PCR enters the logarithmic phase must be calculated. This cycle is called the threshold cycle (CT). The CT cycle is where the fluorescence of products exceeds a threshold limit. To compare initial sample amounts, CT values of samples are compared with each other. The quantitative expression of a gene can be measured using a standard curve or by comparing CT values. In the CT comparison method, the amplification efficiency of the target gene and reference gene should be close to each other. The threshold cycle (CT) for samples was calculated by the instrument. Changes in sample expression for APPL1 and adiponectin genes were calculated using Rest software.

Sequence of primers of adiponectin genes Forward primer: AGATGGCACTCCTGGAGAGAAG Reverse primer: ACATAAGCGGCTTCTCCAGGCT

Sequence of primers of APPL-1 genes Forward primer: TCCGTGTGATCTACGAGCGCAT Reverse primer: GCCAAGACATCGTCGGAGTAGT

2.11 Data Analysis

Descriptive statistics (mean and standard deviation) were used to describe the data. The Shapiro-Wilk test was used to determine normal distribution of data and Levene's test for variance homogeneity. Two-way analysis of variance and Tukey's post hoc test were used for inferential statistics to compare differences between groups. The significance level (P-Value) was considered as $p \leq 0.05$ in all measurements.

Statistical analysis of adiponectin and APPL1 gene expression was performed using SPSS 26 software. Additionally, graphs were drawn using EXCEL software. The raw data was first transformed into an analyzable form using the 2^-ΔΔCt formula, followed by statistical analysis.

3. Results

Table 1 shows the mean and standard deviation of the study groups.

Table 1. Descriptive Variables in Research Groups

Groups	Mean±SD	
	Adiponectin	APPL-1
FLCG	0.64±0.19	0.75±0.11
FLLSG	0.87±0.25	1.07±0.32
FLAEG	1.9±0.38	1.52±0.35
FLAELS	1.56±0.28	2.00±0.38

FLCG: Fatty liver control group, FLLSG: Fatty liver with Lactobacillus supplementation group, FLAEG: Fatty liver with aerobic exercise group, FLAELS: Fatty liver with combined aerobic exercise and Lactobacillus supplementation group

Table 2 Shows Two-way analysis of variance test results for Adiponectin and APPL-1. The results of two-way analysis of variance for adiponectin (P=0.000) and APPL-1 (P=0.000) showed significant differences between groups. The results of Bonferroni post hoc test for adiponectin (Figure 1) showed no significant difference between the control group and the supplement group (p=0.401). However, aerobic exercise and aerobic exercise-supplement groups showed significant differences compared to the control group (p=0.001). Additionally, no significant difference was observed between the supplement group and the aerobic exercise group (p=0.038), but a significant difference was observed between the supplement group and the exercise-supplement group (p=0.001). No significant difference was observed between the aerobic exercise group and the aerobic exercise-supplement group (p=0.0262). The results of Bonferroni post hoc test for APPL-1 (Figure 2) showed no significant difference between the control group and the supplement group (p=0.200). However, aerobic exercise and aerobic exercise-supplement groups showed significant differences compared to the control group (p=0.001). Additionally, no significant difference was observed between the supplement group and the aerobic exercise group (p=0.035), but a significant difference was observed between the supplement group and the exercise-supplement group (p=0.001).

Table 2. Two-way analysis of variance test results for Adiponectin and APPL-1

Variable		Sum of Square	df	F	Eta coefficient	Sig
Adiponectin	Groups	4.30	3	16.03	0.63	0.000*
	Error	2.34	28	-	-	-
	Total	44.34	32	-	-	-
APPL-1	Groups	7.17	3	24.36	0.72	0.000*
	Error	2.73	28	-		-
	Total	67.26	32	-		-

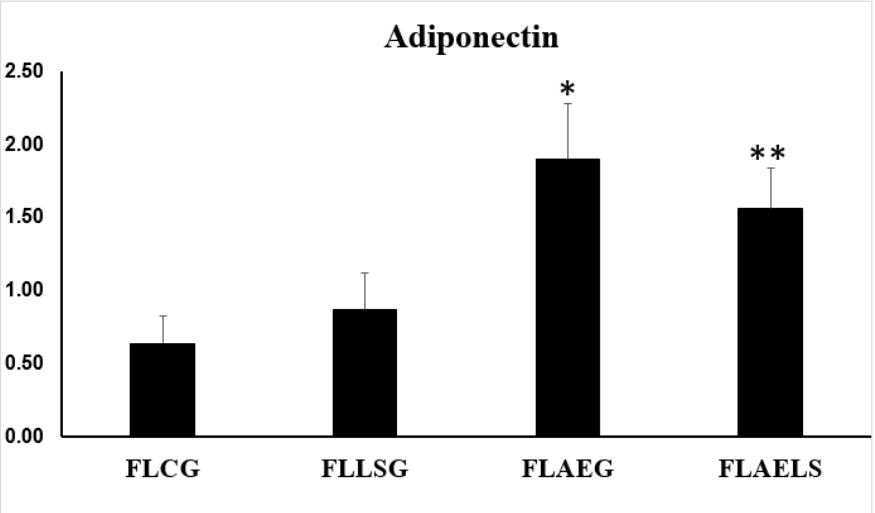

Figure 1. Pairwise comparison of groups for adiponectin

*: significant difference between the FLAEG and the FLCG
**: significant difference between the FLAELS and the FLCG

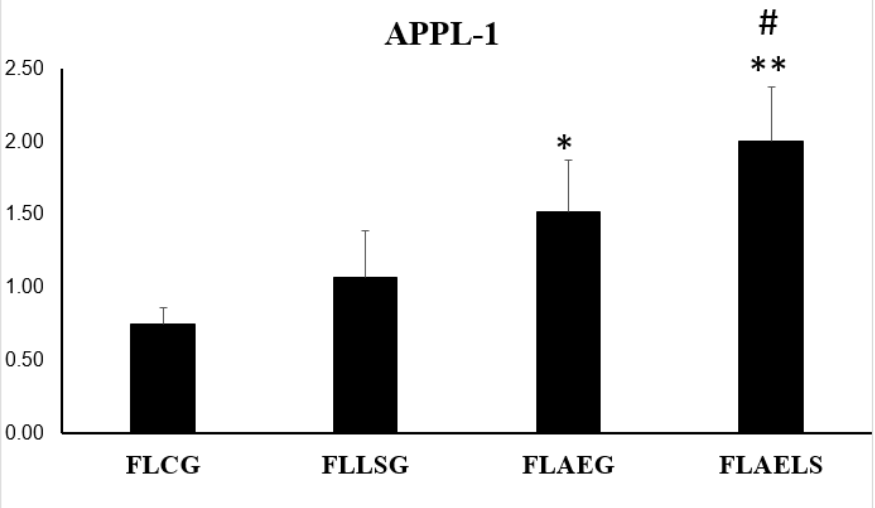

Figure 2. Pairwise comparison of groups for APPL-1

*: significant difference between the FLAEG and the FLCG
**: significant difference between the FLAELS and the FLCG
#: significant difference between the FLAEG and FLAELS
FLCG: Fatty liver control group, FLLSG: Fatty liver with Lactobacillus supplementation group, FLAEG: Fatty liver with aerobic exercise group, FLAELS: Fatty liver with combined aerobic exercise and Lactobacillus supplementation group

4. Discussion and Conclusion

The present study investigated the effects of aerobic exercise and Lactobacillus supplementation on adiponectin and APPL1 gene expression in liver tissue of rats with fatty liver disease. The results demonstrate that aerobic training positively influences adiponectin gene expression, which aligns with previous findings (30, 31). Adiponectin, an adipose tissue-derived hormone, plays a crucial role in liver metabolism and health. This hormone exhibits anti-inflammatory and insulin-sensitizing properties and is significant in the pathophysiology of non-alcoholic fatty liver disease (NAFLD). An inverse relationship between adiponectin levels and fatty liver disease severity has been emphasized (32). Adiponectin regulates glucose and lipid metabolism through activation of various

signaling pathways, including Adipor1 and Adipor2. This hormone enhances fatty acid oxidation and inhibits hepatic lipogenesis, leading to reduced hepatic fat accumulation. These effects are mediated through the activation of AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptors (PPAR) (33). Additionally, adiponectin modulates inflammatory responses and increases anti-inflammatory cytokine production, which is crucial in chronic hepatic inflammation. Recent studies have identified aerobic exercise as an effective intervention for increasing hepatic adiponectin gene expression. Guo et al. (2022) demonstrated that after eight weeks of aerobic exercise, adiponectin levels significantly increased in mice with fatty liver. This elevated adiponectin expression activates the AMPK pathway, improving lipid metabolism and reducing hepatic fat accumulation. Adiponectin also stimulates mitochondrial biogenesis through the LKB1-AMPK-PGC-1α axis, which is vital for lipid metabolism regulation and insulin sensitivity (31). Research has shown that combining aerobic exercise with Lactobacillus supplementation positively affects adiponectin increase (34, 35). These effects may be mediated through improved gut health, as probiotics can modulate gut microbiota and lead to short-chain fatty acid (SCFA) production, enhancing insulin sensitivity. SCFAs can also promote adiponectin secretion by improving intestinal barrier function. The combination of exercise and probiotics creates a synergistic effect leading to enhanced metabolic benefits. Regarding APPL1 expression, our results indicate that aerobic exercise positively influences APPL1 gene expression in liver tissue of fatty liver-affected rats. These findings align with previous evidence (36-38), although some studies have reported different outcomes (39). APPL1, a key protein in high-density lipoproteins, plays a significant role in lipid metabolism and cholesterol transport to the liver. Low levels of HDL and APPL1 are associated with fatty liver disease, and increasing this protein's levels may contribute to improved liver health. Aerobic exercise also affects Akt phosphorylation regulation, which is involved in glucose metabolism and insulin signaling (40, 41). Recent studies have shown that physical activity can increase hepatic APPL1 expression, contributing to positive metabolic outcomes. The combination of aerobic exercise and Lactobacillus supplementation showed a positive effect on APPL1 gene expression. Multiple studies have demonstrated a synergistic effect between probiotic supplementation and physical activity, leading to significant increases in APPL1 expression (42).

The results of the present study demonstrated that aerobic exercise combined with Lactobacillus supplementation, as two beneficial factors, significantly increased the gene expression of adiponectin and APPL1 in rats with non-alcoholic fatty liver disease. Based on the current findings, it can be concluded that Lactobacillus, together with aerobic exercise, can play a crucial role in improving metabolic processes, particularly in the context of obesity and liver health, by upregulating the expression of the adiponectin and APPL1 genes.

One of the primary limitations of this study is the use of a rodent model, which, while providing important mechanistic insights, may not fully replicate the complexity of non-alcoholic fatty liver disease (NAFLD) in humans. The exclusive use of male Wistar rats also raises concerns regarding the generalizability of the findings across different sexes and species. Additionally, the study's short duration limits our understanding of the long-term effects of aerobic exercise and Lactobacillus supplementation on liver gene expression. Variability in individual responses to exercise and probiotic interventions was not explored, and environmental factors, such as stress and dietary influences, could have impacted the results. Finally, the study lacks a detailed analysis of other potential metabolic pathways affected by the interventions, which could provide a more comprehensive understanding of the mechanisms involved.

Future research should consider using both male and female subjects to examine potential sex-specific differences in response to aerobic exercise and probiotic supplementation. Longitudinal studies are needed to determine the sustained effects of these interventions on liver health and overall metabolic outcomes. Exploring the molecular mechanisms underlying the observed gene expression changes, particularly focusing on other pathways involved in lipid metabolism and inflammation, would provide a deeper understanding of the therapeutic potential. Moreover, translating these findings to human clinical trials is essential to validate the efficacy and safety of combined exercise and probiotic regimens in treating or managing NAFLD. Investigating the optimal dosage and timing of probiotics in combination with various forms of exercise could also refine these strategies for clinical application.

The findings of this study have several important implications for non-pharmacological management strategies of NAFLD. Incorporating structured aerobic exercise and probiotic supplementation into standard treatment protocols could offer a holistic and accessible approach to improving liver health and metabolic function. Public health initiatives may benefit from promoting regular physical activity alongside dietary modifications that include probiotics to enhance gut-liver axis interactions. Furthermore, clinicians could consider

personalized exercise and dietary plans for patients at risk of or suffering from NAFLD, tailoring interventions to maximize metabolic and hepatic outcomes. These results also underscore the need for collaborative efforts between healthcare providers and fitness professionals to create comprehensive lifestyle programs aimed at reducing the burden of fatty liver disease.

Authors' Contributions

Z. N. B. and M. G. both contributed significantly to the design and execution of this study. Z. N. B. led the experimental setup, including the implementation of aerobic exercise protocols and administration of Lactobacillus supplementation, as well as overseeing the surgical procedures and liver tissue sample collection. M. G. managed the genetic analysis, including Real-Time PCR experiments and interpretation of gene expression data. Both authors collaborated on the data analysis using statistical methods and co-authored the manuscript, ensuring that all findings and conclusions were accurately reported. They both reviewed and approved the final version of the manuscript and are accountable for the integrity of the work.

Declaration

In order to correct and improve the academic writing of our paper, we have used the language model ChatGPT.

Transparency Statement

Data are available for research purposes upon reasonable request to the corresponding author.

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Declaration of Interest

The authors report no conflict of interest.

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Ethics Considerations

The study protocol adhered to the principles outlined in the Helsinki Declaration, which provides guidelines for ethical research involving human participants. The study protocol was approved by the Ethics Committee of Islamic Azad University – Science and Research Branch (IR.IAU.SRB.REC.1403.192).

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