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RESEARCH ARTICLE

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# The effect of eight weeks of interval training combined with vitamin E supplementation on plasma levels of Betatrophin in men with nonalcoholic fatty liver disease

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## Abstract

**Introduction:** The aim of the present study was to investigate the effect of eight weeks of interval training combined with vitamin E supplementation on plasma betatrophin levels in men with nonalcoholic fatty liver disease.on plasma betatrophin levels in men with nonalcoholic fatty liver disease.

**Methods**: 40 middle-aged men with nonalcoholic fatty liver disease were purposively selected and then randomly divided into 4 groups: interval training, vitamin E, interval training + vitamin E, and control. The exercise intervention was performed for eight weeks, with a frequency of three sessions per week and an intensity of 50-75% of heart rate reserve based on the principle of gradual overload. The vitamin E group consumed vitamin E tablets at a dose of 400 mg daily. Blood sampling was performed 48 hours before and after the exercise period in all groups and simultaneously, and plasma betatrophin levels were measured by ELISA protein assay. One-way analysis of variance (ANOVA) was used to compare variables in the study groups.

**Results**: The results showed that eight weeks of interval training alone and in combination with vitamin E consumption led to a significant decrease in plasma betatrophin levels ($P < 0.05$), while vitamin E consumption alone had no significant effect on the levels of this protein ($P > 0.05$).

**Conclusions:** According to the results, it is recommended that people with non-alcoholic fatty liver disease benefit from intermittent exercise combined with vitamin E consumption to increase fat metabolism and consequently prevent their storage and accumulation, especially in liver tissue.

**Key Words:** NAFLD, interval training, betatrophin, vitamin E

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## 1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is defined as the accumulation of fat exceeding 5% of liver weight [1]. It is the most common liver disorder in developed countries and is closely associated with obesity, insulin resistance, and metabolic syndrome [2]. NAFLD is also strongly linked to disturbances in hepatic lipid metabolism. These disturbances—including an imbalance in fatty acid uptake, synthesis, and oxidation can lead to lipid accumulation in the liver, which is a hallmark of NAFLD. This accumulation may ultimately result in inflammation, cellular injury, and fibrosis, potentially progressing to non-alcoholic steatohepatitis (NASH) and cirrhosis [3].

Betatrophin, also known as TD26, lipoprotein lipase inhibitor, and ANGPTL8, is a novel bioactive peptide that is primarily secreted by adipose tissue and the liver and plays an important role in lipid metabolism. Increased expression of betatrophin elevates serum triglyceride levels and inhibits lipoprotein lipase activity [4]. Betatrophin likely inhibits lipoprotein lipase (LPL) activity through the cleavage of angiopoietin-like protein 3 (ANGPTL3) and the release of its N-terminal domain. Inhibition of LPL impairs triglyceride (TG) clearance, ultimately leading to a marked increase in serum TG levels [5].

The "two-hit" hypothesis has been proposed in the pathogenesis of NAFLD. According to this theory, the first hit involves the accumulation of triglycerides in hepatocytes, leading to hepatic steatosis. The second hit involves oxidative stress and lipid peroxidation, which cause mitochondrial dysfunction; subsequently, hepatic stellate cells proliferate and contribute to hepatocellular injury, inflammation, and fibrosis. Based on this hypothesis, betatrophin appears to play a significant role in the onset and progression of NAFLD [6].

Vitamin E functions as an antioxidant in the body and protects cells against damage. Given that previous studies have shown oxidative stress to play a major role in the pathogenesis of NAFLD [7], vitamin E may exert a protective effect in this condition [8]. Recently, the use of vitamin E has attracted considerable attention due to its potential to prevent the formation or increase of free radicals in NAFLD; however, there is still no consensus regarding the optimal dosage and duration of supplementation, and further studies are needed.

Physical activity, especially interval training, is among the effective approaches in the treatment of fatty liver disease. Exercise helps reduce liver fat, improve insulin sensitivity, and decrease inflammation [9]. It has also been shown that physical activity can reduce liver injury in NAFLD by lowering liver enzymes such as ALT and AST, thereby preventing disease progression [10]. Despite extensive research on the effects of exercise on fatty liver disease, the combined effect of interval training and vitamin E supplementation on NAFLD has not yet been sufficiently investigated. Therefore, the present study aimed to examine the effect of eight weeks of interval training combined with vitamin E supplementation on plasma betatrophin levels in men with non-alcoholic fatty liver disease.

## 2. Methods

### *2.1. Participants*

The present study employed a quasi-experimental, applied research design to investigate the effects of an eight-week interval training program combined with Vitamin E supplementation on plasma betatrophin levels in men with non-alcoholic fatty liver disease (NAFLD). The statistical population comprised men aged 45 to 60 years diagnosed with non-active NAFLD in Ahvaz, Iran. Following a screening process conducted in collaboration with the Fatty Liver Association, 40 participants were selected via convenience sampling. The participants were divided into the following groups: 1)Interval Training Group, 2)Vitamin E Group, 3)Combined Group (Training + Vitamin E) and 4)Control Group.

### *2.2. Study design*

blood samples were taken 48 hours before the start of the exercise period and 48 hours after the last training session in oll groups. The groups received intervention according to specific protocols.

The criteria for entering the research can be mentioned the No participation in sports training for at least the past six months, age range of 60 to 74 years for subjects, no use of medications known to affect inflammatory markers or cardiovascular function, no smoking or alcohol consumption, no cardiovascular disease, high blood pressure, respiratory disease, or other diseases.

tehe Exclusion Criteria also inclufe the injury or illness, withdrawal, unwillingness to cooperate, unwillingness to perform the training protocol, absence of more than three training sessions, presence of symptoms related to the need to stop sports activities such as chest pain and other symptoms in accordance with the ACSM guidelines on sports withdrawal syndrome. Due to the nature of the intervention, blinding of the researcher and subjects was not possible. However, the blood sample analyzer was blinded to group allocation.

### *2.3. Sample size calculation*

The sample size was determined using Cochran's formula, accounting for a 5% margin of error based on the mean (15.63) and standard deviation (3.15) of the primary variable, betatrophin. Participants were then randomly assigned into four experimental groups (n=10 per group).

### *2.4. Nutritional intervention / Supplementation protocol*

Participants in both the Vitamin E and the Combined (Training + Vitamin E) groups were administered a daily oral dose of 400 mg of Vitamin E for a duration of eight consecutive weeks.

### *2.5. Exercise protocol*

The interval training program was implemented over eight weeks with a frequency of three sessions per week. Each 60-minute session consisted of a 15-minute general and specific warm-up, 35 minutes of interval running, and a 10-minute cool-down (comprising stretching and light jogging).

The interval component involved seven repetitions of 5-minute running bouts, interspersed with 2.5-minute active recovery periods. Exercise intensity was prescribed based on the Karvonen formula, utilizing the Heart Rate Reserve (HRR). Initial intensity in the first week was set at 50% of HRR. Following the principle of progressive overload, the intensity was increased by 5% each week, reaching 70% of HRR during weeks five and six, and concluding at 75% of HRR in weeks seven and eight. Exercise intensity was strictly monitored using Polar heart rate monitors attached to the participants' wrists. Participants were instructed to refrain from any other organized physical activities throughout the eight-week study period. Based on the principle of gradual overload, the training intensity was increased by 5% each week until the training intensity reached 70% of the heart rate reserve in weeks five and six, and finally, in weeks seven and eight, the training intensity ended with 75% of the heart rate reserve [11].

### *2.7. Blood Sampling and Biochemical Analysis*

Blood samples were collected by a laboratory technician 48 hours prior to the initial training session (pre-test) and 48 hours following the final training session (post-test) from all participants across the four groups. Blood collection was performed after a 12-hour overnight fast in a resting state; 5 mL of blood was drawn from the left anterior antecubital vein in a seated position. The samples were immediately transferred into sterile tubes containing EDTA as an anticoagulant.

The collected blood was centrifuged at 3,000 rpm for 10 minutes to isolate the plasma. The resulting plasma was transferred into 1-mL microcentrifuge tubes and stored in a freezer at −80C for subsequent analysis. Following the completion of the post-test phase, all frozen samples were thawed on the same day, and biochemical analyses were conducted according to established protocols. Plasma betatrophin levels were quantified using an Enzyme-Linked Immunosorbent Assay (ELISA) kit (human, antibodies.com) with a sensitivity of 28.125 pg/ml.

### *2.8. Ethical Considerations*

Since this study involved human participants and long-term interventions (physical exercise and nutritional supplementation), it was conducted in strict accordance with ethical research principles. Ethical approval was obtained from the Ethics Committee of Islamic Azad University, Ahvaz Branch (Ethics ID:IR.IAU.AHVAZ.REC.1404.182).

### *2.9. Statistical analysis*

Data were expressed as the mean±standard deviation (SD). The normality of the data distribution was assessed using the Shapiro-Wilk and Kolmogorov-Smirnov tests, and the homogeneity of variances was verified using Levene's test. To compare the variables among the study groups, a one-way analysis of variance (ANOVA) followed by Tukey's post-hoc test was employed. All statistical analyses were performed using SPSS version 23, with the significance level set at $p<0.05$.

## 3. Results

### Changes in plasma betatrophin levels

To investigate the effect of eight weeks of interval training on plasma betatrophin levels in men with nonalcoholic fatty liver disease, one-way analysis of variance (ANOVA) was used. As the results of this test are shown in Table 2, a significant difference in plasma betatrophin levels was observed between the groups (P=0.001).

to identify significant differences between the groups, Tukey's post-hoc test was employed. Based on the results of this test, eight weeks of interval training had a significant effect on plasma betatrophin levels in men with non-alcoholic fatty liver disease (NAFLD), resulting in a significant reduction (P=0.012). In contrast, eight weeks of vitamin E supplementation did not exert a significant effect on plasma betatrophin levels in this population, with no significant changes observed (P=0.179).

Furthermore, it was observed that eight weeks of combined interval training and vitamin E supplementation had a significant effect on plasma betatrophin levels in men with NAFLD, leading to a significant decrease (P=0.009). Additionally, the effect of the combined intervention (interval training


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plus vitamin E) showed no significant difference compared to interval training alone (P=0.153); however, a significant difference was observed when compared to vitamin E supplementation alone (P=0.023). The comparison of betatrophin levels across the four groups is illustrated in Figure 1.

Table 1: Results of analysis of variance (ANOVA) to compare plasma betatrophin levels between groups

| Sig | F | Mean square | df | Sum of squares | Source |
|---|---|---|---|---|---|
| 0.001 | 27.759 | 187.237 | 3 | 561.713 | **Between Groups** |
| | | 6.745 | 36 | 242.835 | **Within Groups** |
| | | | 39 | 804.548 | **Total** |

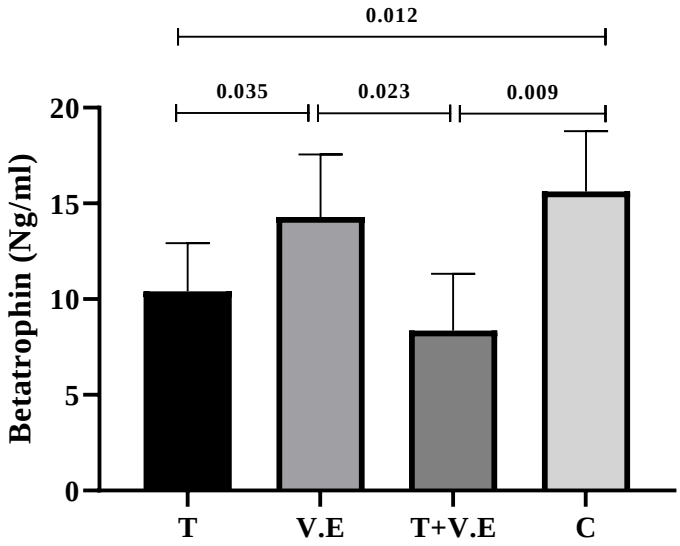


Figure 1: Comparison of betatrophin changes in between groups.
a significant between-group difference ($p < 0.05$).
T: training group, V.E: vitamin E group, T+V: training+ vitamin E group, C:control group

## 4. Discussion

The present study demonstrated that eight weeks of interval training resulted in a significant reduction in plasma betatrophin levels in men with non-alcoholic fatty liver disease (NAFLD). Betatrophin, a protein secreted by the liver and adipose tissue, plays a crucial role in glucose and lipid metabolism. Consequently, it has been suggested that betatrophin may serve as a potential therapeutic target in patients with metabolic disorders, such as NAFLD and diabetes [12]. However, the systemic response to the secretion of this hormone and its precise mechanism of action remain to be fully elucidated. Zhang et al. [13] demonstrated that hepatic fat content increases alongside rising serum betatrophin levels, suggesting that serum betatrophin could serve as a predictive biomarker for NAFLD.

The cellular mechanisms by which exercise influences betatrophin levels are not yet fully understood. Given that betatrophin levels decrease following weight loss induced by dietary interventions, it is plausible that exercise may also reduce betatrophin levels through weight reduction. Furthermore, research indicates that satiety increases betatrophin levels, whereas hunger and caloric restriction lead to its depletion. Additionally, it has been reported that AMPK (adenosine monophosphate-activated protein kinase) activation in the liver is diminished during obesity and physical inactivity. Exercise may induce a state of caloric restriction within the tissue and potentially reduce hepatic betatrophin production by enhancing the activation of the AMPK/PPARα (peroxisome proliferator-activated receptor alpha) signaling pathway. Since betatrophin expression is upregulated by the hepatic liver X receptor (LXR), exercise through AMPK-mediatedphosphorylation of PPARα may inhibit the expression of SREBP/LXR1 transcription factors, thereby suppressing betatrophin expression [14].

Extensive research has demonstrated that regular physical activity particularly exercise training, defined as a planned, structured, repetitive, and goal-oriented

form of physical activity—induces beneficial intrahepatic and extrahepatic adaptations in patients with NAFLD [15]. These advantages encompass improvements in hepatic steatosis, alterations in body composition, enhanced physical fitness, reduction in cardiovascular risk markers, and improved health-related quality of life [16]. Crucially, many of these adaptations, including the reduction of hepatic fat content, may occur independently of body weight and even in the absence of significant weight loss [17]. Exercise is associated with multiple mechanisms involved in the management of NAFLD and the attenuation of betatrophin levels.

AMPK (adenosine monophosphate-activated protein kinase) serves as a critical cellular energy sensor that is activated under conditions of metabolic stress. It exists as a heterotrimeric complex consisting of a catalytic subunit (α) and two regulatory subunits (β and γ). AMPK plays a pivotal role in maintaining systemic energy homeostasis and exerts specific hepatic effects on lipogenesis, fatty acid oxidation, glycogenolysis, and gluconeogenesis. In patients with NAFLD, AMPK activity is pathologically diminished, contributing to excessive hepatic lipid accumulation [18]. Animal models of NAFLD indicate that exercise modulates the AMPK pathway, thereby reducing hepatic fat accumulation by inhibiting lipogenesis and promoting fatty acid oxidation [19-22].

As the primary site for both lipogenesis and fatty acid oxidation, the liver plays a central role in lipid metabolism; specifically, hepatic lipid-derived energy production occurs via mitochondrial beta-oxidation [23]. However, mitochondrial dysfunction inked to both physical inactivity and obesity [24] reduces mitochondrial oxidative capacity. This deficiency leads to incomplete beta-oxidation and the subsequent accumulation of metabolic byproducts, such as ceramides and diacylglycerols (DAGs) [25]. While hepatic triglycerides themselves do not directly induce hepatic insulin resistance, it is hypothesized that the accumulation of these aforementioned metabolic intermediates disrupts insulin receptor signaling through various mechanisms, serving as a critical factor in the pathogenesis of hepatic insulin resistance [26]. Regular exercise has been shown to enhance mitochondrial oxidative capacity and increase mitochondrial content, which is closely associated with improved cardiorespiratory fitness. In fact, cardiorespiratory fitness exhibits an inverse relationship with hepatic steatosis, and improvements in physical fitness are independently correlated with the resolution of steatosis [27].

Oxidative stress arises from an imbalance between the production and accumulation of reactive oxygen species (ROS), ultimately impairing the capacity for detoxification and the clearance of these reactive products [28]. ROS play a pivotal role in the development of NAFLD and its progression to non-alcoholic steatohepatitis (NASH) through numerous complex mechanisms that contribute to cellular injury, inflammation, and fibrosis [29]. These mechanisms include lipid peroxidation, mitochondrial dysfunction, activation of inflammatory pathways, and insulin resistance, all of which exacerbate hepatic steatosis and inflammation [30]. Furthermore, ROS induce epigenetic modifications, disrupt bile acid homeostasis, and affect the gut-liver axis, collectively leading to hepatic inflammation and injury [31].

Exercise training suppresses excessive ROS production by upregulating several essential antioxidant enzymes and anti-inflammatory mediators in NAFLD [10]. Nuclear factor erythroid 2-related factor 2 (Nrf2), a transcription factor critical for the upregulation of endogenous antioxidant defenses, plays a vital role in regulating the systemic antioxidant response and defending against oxidative stress; notably, Nrf2 can be activated by exercise training in human skeletal muscle [32]. The activation of the Nrf2 pathway enhances antioxidant capacity, reduces inflammation, improves insulin sensitivity, attenuates hepatic steatosis and inflammation, and slows the progression of NAFLD [33].

Vitamin E, a well-recognized antioxidant known for preventing lipid peroxidation, scavenging ROS, and protecting cellular membranes from oxidative damage, may counteract the effects of ROS in patients with NAFLD. It has been demonstrated that Vitamin E can significantly reduce hepatic steatosis. More recent evidence suggests that Vitamin E may even reverse hepatic fibrosis and mitigate adverse hepatic outcomes [34]. However, in the present study, Vitamin E supplementation alone had no significant effect on betatrophin levels or liver enzymes, and no significant difference was observed between the effects of eight weeks of interval training alone and the combined intervention of interval training with Vitamin E. This discrepancy may be attributed to the dosage and duration of Vitamin E administration. For instance, Sialal et al. [35] evaluated 247 non-diabetic and non-cirrhotic adults with NAFLD in a clinical trial, where participants received 800 IU/day of Vitamin E for 96 weeks, resulting in improved histological features regarding steatosis, inflammation, hepatocyte ballooning, and fibrosis. In contrast, the current study utilized a lower dosage of 400 IU/day for a duration of only eight weeks.


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## 5. Conclusion

In the present study, plasma betatrophin levels were significantly reduced following eight weeks of interval training, both as a standalone intervention and when combined with Vitamin E supplementation, in individuals with non-alcoholic fatty liver disease (NAFLD). Given the role of betatrophin in modulating hepatic lipogenesis and subsequently preventing lipid accumulation within hepatocytes, it can be concluded that interval training, particularly when combined with Vitamin E, plays a crucial role in preventing hepatic fat accumulation by lowering betatrophin levels, thereby potentially inhibiting the progression of NAFLD.

The present study was conducted on an elderly population, and due to the inherent challenges of researching this demographic, the sample size was limited to 10 participants per group. Furthermore, strict dietary control and the implementation of isocaloric diets across groups were not feasible, which constitute notable limitations of this research. Consequently, it is recommended that future studies incorporate rigorous dietary monitoring and control to minimize nutritional confounding factors. Additionally, given the established correlation between betatrophin and enzymes involved in lipid metabolism, future investigations should consider evaluating lipid-metabolizing enzymes, such as lipoprotein lipase (LPL), alongside the effects of exercise and Vitamin E on betatrophin levels to provide a more comprehensive understanding of these metabolic pathways.

## 6. Highlights

According to the findings of the present study, it is recommended that people with nonalcoholic fatty liver disease use interval training alone or in combination with vitamin E supplementation to control fatty liver disease and, consequently, prevent its complications.

## Statements

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### Conflicts of Interest

The authors declare no conflict of interest in the present study.

### Authors' Contributions

Conceptualization: J.B., M.B.,; Methodology: J.B., M.B.,; Formal analysis: J.B., M.B.; Investigation: J.B., M.B.; Writing - original draft: J.B., M.B.; Writing review & editing: J.B., M.B.; Supervision: M.B.

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