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The effect of running and starvation interventions on atherogenic index and Xbp1 gene expression in the endoplasmic reticulum of liver in non-alcoholic fatty liver rats

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Abstract

Background: Running and starvation can have a positive effect on the reticulophagy of the liver tissue. The purpose of this research was to investigate the effect of running and starvation interventions on the atherogenic index and Xbp1 gene change in the liver endoplasmic reticulum of non-alcoholic fatty liver rats (NAFLD).

Methods: Thirty obese male Wistar rats aged 18-20 weeks with an average body weight of 348 ± 25.53 grams, after one week of familiarization with the laboratory environment, were randomly divided into six groups (n=5 per group): 1) starvation, 2) three days of training, 3) five days of training, 4) three days of training plus starvation, 5) five days of training plus starvation, and 6) the control group. All fatty liver animal models had free access to water and standard food pellets (10 gr per 100 g of mouse body weight). The statistical test of one-way analysis of variance was used at a significance level of less than 0.05, and the LSD post-hoc test was used to compare research groups.

Results: According to the experimental results and statistical analyses (One-way analysis of variance), a significant decrease was noticed in the ratio of lipoproteins (VLDL/HDL and LDL/HDL) in all experimental groups compared to the control group. Also, a significant decrease was observed in the expression of XBP1 and CHOP genes in animals doing 3 and 5 days of exercise alone or along with starvation.

Conclusion: Regular exercise for 3 and 5 days per week with starvation can possibly reduce the activity of the genes involved in endoplasmic reticulum stress in NAFLD patients.

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Introduction

The liver is a complex organ that performs many physiological functions (1), including the synthesis, oxidation, and transport of free fatty acids (FFA), triglycerides (TG), cholesterol, and bile acids (BA) and plays a key role in lipid homeostasis (2). These processes act through various pathways that lead to oxidative stress, chronic inflammation, and insulin resistance (3). The reported prevalence of non-alcoholic fatty liver (NAFLD) in Western countries is between 30% and 46%. This disease has also spread in eastern countries and become one of the public health concerns in these regions (4). Non-alcoholic fatty liver includes a spectrum of liver injuries from steatosis to nonalcoholic steatohepatitis (NASH), which can lead to fibrosis (5). People with NAFLD are also at an increased risk of cardiovascular disease, type 2 diabetes, and obesity-related mortality. The exact mechanisms of NAFLD are still not well understood (6). The "multiple hit hypothesis" is currently the most recognized theory for explaining the development and progression of the disease. The initial shock leads to simple steatosis, while subsequent shocks (e.g., mitochondrial dysfunction, oxidative stress, adipocytokine changes, lipid peroxidation, Kupffer cell activation, etc.) lead to hepatic inflammation and apoptosis, finally culminating in simple steatosis (7).

Recently, based on accumulated data, it has been shown that the disruption of endoplasmic reticulum (ER) homeostasis, or ER stress, is involved in both the development of steatosis and its progression to NASH (8). Endoplasmic reticulum is a membrane-bound organelle that provides a specialized environment for the production and post-translational modification of secretory and membrane proteins, lipid biosynthesis, and intracellular Ca2+ homeostasis (9). Some physiological and pathological conditions, including temperature and pH changes and accumulation of damaged DNA, can cause ER stress (10). Endoplasmic reticulum stress can be divided into three types, including the unfolded protein response (UPR), ER overload response, and sterol regulatory elements along with regulatory responses with protein mediators. Endoplasmic reticulum stress is commonly referred to as UPR and occurs when folded or unfolded proteins are accumulated in the ER, activating a stress signal that is transmitted through the ER membrane to the nucleus (11). Findings show that membrane receptors on ER recognize the onset of ER stress and initiate the UPR to restore normal ER function. If the stress is prolonged, or the adaptive response fails, apoptotic cell death occurs (12).

As a result of ER stress, cells mainly develop two responses: one leads to cell survival and the other leads to apoptosis (13). Using the survival pathway, cells overcome such adverse effects and maintain homeostasis through the UPR, inhibition of mRNA transcription, increasing the folding capacity of ER, and activating ER-associated protein degradation (ERAD) to restore homeostasis (14). Under chronic or severe ER stress, the normal functions of ER are not recovered, resulting in cell dysfunction and apoptosis (14). Therefore, the ER is considered a quality control checkpoint so that only correctly folded proteins can exit its space and pass through the secretory pathway. Therefore, any event such as starvation and excessive protein synthesis, accumulation of mutant proteins, depletion of ER calcium, or changes in the redox state that disrupts the folding capacity of the ER triggers a physiological response called the UPR. These homeostatic responses induce the production of additional chaperones to increase the folding capacity of ER, enforce protein degradation in ER, slowing down the translation and synthesis of new proteins to reduce protein entry and thus restore the functional balance in the organelle and cells (15). Studies show that silencing the C/EBP homologous protein (CHOP) reduces apoptosis in hepatic cells in alcohol-induced liver disease and cholestasis-induced fibrosis (16). This protein can also regulate the expression of autophagy-related genes in the later stages of starvation and prevent the occurrence of autophagy and imminent apoptosis (17). However, the role of CHOP in NAFLD is debatable (18). Some studies found that CHOP can prevent NAFLD (19,20), and other experiments on mice showed that CHOP could be associated with many ER stress-related diseases (21).

Chronic ER stress interferes with body metabolism by activating lipogenesis and increasing VLDL (22). Research is ongoing to provide non-pharmacological alternatives to reduce the risk of NAFDL. Exercise is one of the ways to replace drugs as a therapeutic strategy in this and other diseases. Houghton et al (23) Stefano et al (24) and Bacchi et al. (25) suggested that both aerobic and resistance exercises had similar effects on liver TG in patients with NAFLD. These studies show that different types of exercise help mitigate the risk of NAFLD. Also, interventional studies have shown that regular exercise can reverse ER disorders (26), and UPR activation has been reported to reduce ER stress (27,28). The UPR is an important pathway modulating fatty acid oxidation and lipogenesis (29). Furthermore, chronic fasting conditions in mice have been shown to activate the UPR to regulate lipid metabolism (30). Studies have shown that XBP1 regulates the genes involved in various cellular processes, such as ER stress response, secretory function, lipid metabolism, glucose homeostasis, and inflammation (31,32). Furthermore, XBP1 regulates the expression of the genes involved in fatty acid synthesis, augmenting hepatic lipogenesis (33). Several studies have shown that XBP1 plays an important role in adipocyte differentiation by regulating morphological and functional changes during adipogenesis (34). The importance of XBP1s in lipid biosynthesis has been demonstrated by boosting triglyceride (TG) biosynthesis and causing abnormal fat accumulation (35).

Chronic starvation in mice has been shown to activate the UPR to regulate lipid metabolism (36). Also, studies show that exercise upregulates hepatic XBP1

and SREBP through ER stress signaling, thereby reducing lipid accumulation in NAFLD (37). The contradictions rising from human and animal experiments led us to investigate the effects of aerobic exercise (Running on a treadmill) and 4-week starvation on the activity of the apoptotic pathway triggered by ER stress in the liver of male rats with NAFLD.

Methods

Thirty obese male Wistar rats aged 18-20 weeks with an average body weight of 348 ± 25.53 grams, after one week of familiarization with the laboratory environment, were randomly divided into 6 groups of five: 1) starvation, 2) three days of training, 3) five days of training, 4) three days of training plus starvation, 5) five days of training plus starvation, and 6) the control group.

All fatty liver animal models had free access to water and standard pellet food (10 g of food per 100 g of mouse body weight). All maintenance and euthanizing procedures were carried out in the Animal Science Laboratory of Gorgan University of Medical Sciences. The fasting protocol was applied for one month (Every day and 14 hours per day in the waking cycle: 5.5 p.m. to 5.7 a.m.). In order to induce hunger, the rats in the starvation group were given the same amount of food (10 grams per 100 grams of mouse body weight). The animals under starvation received the same type of food over the remaining 10 hours as other groups.

The entire training course included two stages: familiarization and main training. For this purpose, the test was conducted for 15 minutes for a week and exercise for 45-60 minutes on a treadmill (Either 3 or 5 days a week for 4 weeks). The training on the treadmill started at a 0-degree incline and a speed of 14 meters. After the training sessions, the speed of the treadmill with zero incline reached 16 and 18 meters per minute (38).

Regarding biochemical factors, HDL was measured by an enzymatic method and LDL and VLDL by a calorimetric method using biochemical kits manufactured by Darman Kav and Far Samad companies in Iran. The analyses were conducted on a BS480 auto analyzer. Finally, the ratios of VLDL/HDL and LDL/HDL were calculated.

For molecular investigations at the level of gene expression, RNA was first extracted from tissues in all study groups according to the protocol of Yekta Azma RNA extraction kit (Cat. No: FABRK001, Lot. No: K812320822). Then we measured the quality and quantity of RNA with a Nanodrop device. Next, cDNA synthesis kit of Pars Tous Company (Mashhad, Iran, Parstous.lot: 2156, REF: A101161) was utilized to generate cDNA, which was then used to perform the reverse transcription reaction. Expression levels of XBP1 and CHOP genes were measured using real-time quantitative PCR using SYBER Green qPCR master mix (Cat. No: YT2552, Lot. P2003) using primers manufactured by Pishgam Biotech company. The glyceraldehyde-3-phosphate dehydrogenase (GAPDH) gene was used as a control, and the expression level of the desired gene was calculated with the $2^{-\Delta\Delta CT}$ formula. First, the threshold cycle of the desired gene in each sample was corrected respective to the threshold cycle of the housekeeping gene by subtraction ($\Delta Ct=Ct^{Target}-Ct^{Housekeeping}$). In the next step, the delta Ct of each sample was subtracted from the samples to which it needed to be compared ($\Delta\Delta Ct=\Delta Ct^{Target}-\Delta Ct^{Reference}$). Finally, the reverse value of the obtained number was calculated to the power of two: Target gene/Reference gene ratio = $2^{-\Delta\Delta CT}$ to obtain the relative expression of target genes. The primers used are shown in Table 1. The size of the genes is as follows: C/EBP homologous protein gene ID: DDIT3 (Length: 150 bp) and X-box binding protein 1 gene ID: XBP1 (Length: 601 bp).

Table 1. Sequences of primers used

Genes	Primer sequence (5' → 3')	Number of nucleotides	Amplicon Size(pb)
Chop-F	GAAAGCAGAAACCGGTCCAAT	21	**150**
Chop-R	GGATGAGATATAGGTGCCCCC	21	-
XBP1-F	AAACAGAGTAGCAGCGCAGACTGC	24	**601**
XBP1-R	GGATCTCTAAAACTAGAGGCTTGGTG	26	-
GAPDH-F	CACTGAGCATCTCCCTC ACAA	22	-
GAPDH-R	TGGTATTCGAGAGA AGGGAGG	22	-

Tables 2 and 3 display descriptive statistics (The mean and standard deviation) and inferential statistics (based on one-way analysis of variance, p value, and the LSD follow-up test) used to present data and compare research groups, respectively.

Results

The results obtained (Table 2), showed the lowest mean LDL/HDL and VLDL/HDL ratios belonged to the 5-day training plus starvation group (0.28±0.61 and 0.12±0.286, respectively), indicating the better effects of combined training and fasting. Also, the lowest mean XBP1 gene expression (0.13±0.20) and the highest decrease in mean CHOP expression (0.06±0.15) were seen in the 5-day training plus fasting group. Genes involved in the inflammatory pathway promote autophagy in NAFLD patients and can be modulated by exercise and fasting. And also, the average values of chaperone and XBP1 genes are shown in Figure 1 (A, B).

The results of one-way ANOVA (Table 3) showed a significant change in the ratios of LDL/HDL (P=0.00, F=23.986) and VLDL/HDL (P=0.00, F=23.986), as well as in the expression of CHOP (P=0.00, F=23.986) and XBP1 (P=0.00, F=23.986) genes. Also, the LSD follow-up test showed a significant decrease in the VLDL/HDL and LDL/HDL ratios in all experimental groups compared to the control group (P = 0.001). Also, there was a significant decrease in the expression of XBP1 in the 5-day training and 3- and 5-day training plus starvation groups (P = 0.001) but not in the starvation alone and 5-day training alone groups (P= 0.845 and P = 0.055, respectively). The CHOP gene also showed a significant decrease in all groups except in the starvation alone group (P = 0.580) compared to the control group (P = 0.00).

Table 2. Mean and standard deviation of variables studied in fatty liver rat models

Mean and standard deviation	Starvation group + 5 Days of training	Starvation group + 3 Days of training	5 Days training group	3 Days training group	Starvation group	Control group
VLDL/HDL	**0.12±0.286**	**0.72±0.31**	**0.69±0.21**	**0.94±0.70**	**0.73±0.21**	**2.43±0.43**
LDL/HDL	**0.61±0.28**	**1.23±0.32**	**1.03±0.24**	**1.17±0.69**	**1.79±0.32**	**3.69±0.81**
CHOP	**0.13±0.20**	**0.22±0.22**	**0.30±0.23**	**0.55±0.38**	**1.08±0.15**	**1.00±0.00**
XBP1	**0.06±0.15**	**0.22±019**	**0.35±0.31**	**0.77±0.21**	**0.97±0.43**	**1.00±0.00**

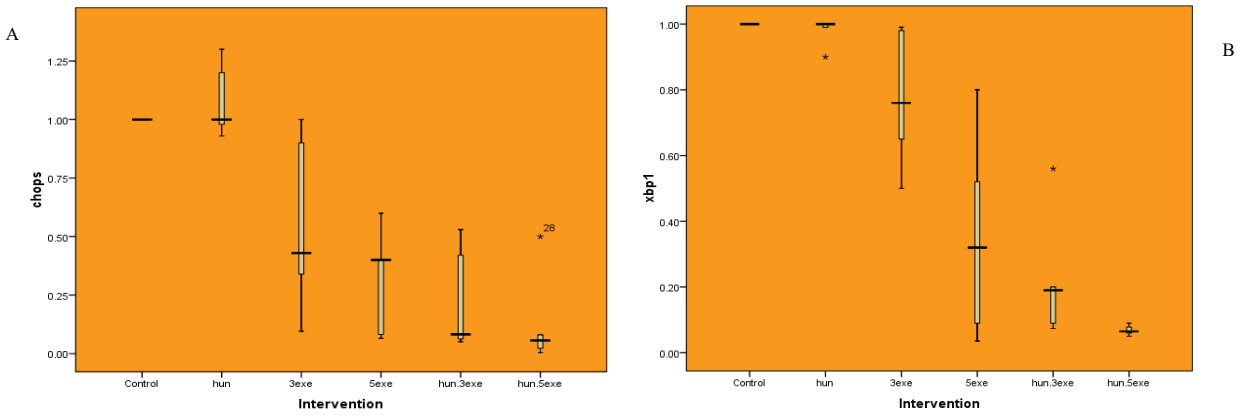

Figure 1: Average graph of CHOP and XBP1 genes

Table 3. One-way analysis of variance results for comparing the means of study variables between groups

Variables	Sources of change	Sum of squares	Mean square	df	f	p
LDL/HDL (Mg/dL)	Intergroup	140.084	60.39	5	23.986	0.000
	Within-group	6.403	0.252	24		
	Total sum	36.240	-	29		
VLDL/HDL (Mg/dL)	Intergroup	14.084	2.817	5	19.269	0.000
	Within-group	3.509	0.146	24		
	Total sum	17.593	-	29		
CHOP (Ng/mol)	Intergroup	4.103	0.821	5	15.340	0.000
	Within-group	1.284	0.053	24		
	Total sum	5.386	-	29		
XBP1 (Ng/mol)	Intergroup	4.063	0.813	5	26.290	0.000
	Within-group	0.742	0.031	24		
	Total sum	4.805	60.39	29		

Discussion

The aim of this study was to investigate the effects of aerobic exercise (Running on a treadmill) and starvation for 4 weeks on the regulation of the apoptotic pathway triggered by ER stress in the hepatocytes of male Wistar NAFLD rats. Regarding XBP1 expression, the highest average was observed in the starvation group, and the lowest average was observed in the starvation + 5 days of training group. The results showed that four weeks of aerobic exercise along with starvation reduced the expression of both XBP1 and CHOP genes, which are involved in the development of NAFLD. The control and starvation groups had the highest average expression of these genes, and exercise decreased their expression levels. Research shows that exercise controls the transcription of XBP1 in the liver (35,36). Various mechanisms can be involved in this regulatory process. Previous studies indicate that the goal of the UPR is to restore the homeostasis and normal function of ER by adaptive mechanisms to upregulate the genes involved in increasing the capacity of ER to degrade proteins (35). When the primary stimuli that cause UPR are long or excessive, UPR-related adaptive mechanisms fail, leading to apoptotic cell death (37).

It has been reported that starvation causes a decrease in nutrients inside the cell and is recognized by brain material-sensing signaling pathways such as mTOR and AMPK pathways, which ultimately stimulate autophagy (39). In addition, p-eiF2α selectively promotes the translation of a number of mRNAs, including ATF4 and IRE1. The activation of IRE1 triggers the modification of XBP1 and subsequent transcription of molecular chaperones and genes involved in ERAD (40). Finally, activated ATF6 undergoes proteolytic cleavage in the Golgi, allowing its mature form to enter the nucleus and induce ER stress-related genes such as ER chaperones and foldases (41). Research findings show that starvation activates the IRE1α-XBP1 route (42), and the combination of fasting, acute resistance training, and protein consumption (Immediately or 1 hour after exercise) increases the serum levels of leucine, insulin, and glucose, as well as the levels of autophagic proteins in skeletal muscles (43,44) but reduces proteins related to the autophagic pathway in the liver (45). It has also been shown that 6 weeks of wheel running suppressed XBP1s mRNA in HFD-fed mice, and similar results were reported in mice after 6 weeks of treadmill training (45). In addition, swimming exercise decreased IRE-1α and XBP1 protein levels and hepatic TG content in rats with NAFLD (46). Lu et al. showed that exercise decreased SREBP-1 induced fat accumulation in the liver through the AMPK pathway and the inhibition of the mammalian target of rapamycin complex 1, which finally relieved ERS (46). Moreover, exercise reduced hepatic lipogenesis via the PERK/ATF4/SREBP pathway (47). These studies suggest that exercise regulates hepatic XBP1 and SREBPs through ER stress signaling and thus reduces fat accumulation in the liver of NAFLD. Exercise also reduces excessive aberrant phosphorylation in the ER, promoting apoptosis and cell death. Also, endurance activity such as swimming, due to the compatibility between transmembrane proteins, alleviates the amount of misfolded or over folded proteins, as the source of stress, in the ER. As a result, stress subsides in the ER.

The results of some studies are not consistent with our findings in the present study. In a study, short-term sports activity such as a one-day sprint or a five-day activity for a week had no effects on the expression of XBP1, ATF6, and PERK proteins, which could be probably due to the short duration (Less than a week) of the sports activity (43,45). It has been suggested that in order to induce the expression of ER-related proteins, the minimum time of sports training should be four weeks (48). It has also been reported that rats with a history of sports activity had less stress symptoms and the expression of UPR-related proteins (XBP1, ATF6) and CHOP gene after resistance training than rats that did not have any sports activity, suggesting that sports activity has a positive effect on reducing stress symptoms (49). Overall, sports activity can be considered a therapeutic strategy to mitigate liver diseases, including NAFLD. The results of the present study showed that NAFLD was associated with the overexpression of XBP1 and CHOP genes, and this increase was significant in the exercise alone and exercise + starvation groups compared to the control group. This can somehow confirm that ER stress is one of the main causes of cell apoptosis in the liver. According to the statistical results of our research, a significant decrease was observed in the ratio of lipoproteins (VLDL/HDL, LDL/HDL) in all experimental groups compared to the control group. In recent years, several clinical trials have shown that starvation is an effective way to reduce fat and regulate lipid profile. Starvation or energy-restricted diets have favorable effects on body weight, total fat mass, and liver fat reduction. In addition, intermittent fasting can improve the biomarkers of systemic inflammation and appetite-regulating hormones (50). A recent finding suggested that exercise was superior to a calorie restriction program in reducing cholesterol biosynthesis. Short-term exercise combined with dietary interventions had a great effect on reducing metabolic risks and fasting insulin levels (50). In a study by Askari et al. in 2012, 8 weeks of aerobic exercise reduced the percentage of subcutaneous fat, total cholesterol, RF, and plasma low-density lipoproteins in non-athletic women (51). Also, in another study by Dadban et al. in 2021, it was shown that 4 weeks of regular aerobic exercise reduced liver lipase activity and thus triglyceride production (VLD L-C and LDL-C). Elevated LDL-C is an independent risk factor for coronary artery disease, while the reduction of LDL-C to 60 mg/dL mitigated the risk of coronary heart disease by 50% within two years. HDL-C transports cholesterol from peripheral tissues to the liver and then directs excess cholesterol to the bile for excretion (52). Our results are consistent with the findings of the aforementioned studies.

In summary, understanding the effects of diet on disease severity is one of the most complex aspects in the management of patients with NAFLD. As a result, evaluating the effects of dietary interventions is challenging because they affect the entire metabolism, making it difficult to isolate specific (Beneficial) effects on the liver. However, a low-calorie low-carbohydrate diet combined with continuous aerobic exercise with repetitions of at least 3 days and up to 5 days could potentially be suitable for the successful "treatment" of NAFLD.

Conclusion

Impaired autophagy may be a critical pathogenic mechanism in NAFLD, highlighting the role of exercise and starvation as important tools in the prevention of this condition. The findings of the present research revealed that the breakdown of lipids in the liver moderated the disease due to an increase in the non-selective autophagy of hepatocytes through endoplasmic reticulum. Running exercise with starvation causes NAFLD rats to activate CHOP and XBP1 genes, leading to apoptosis, obviation of ER stress, and removal of stressed cells. So, this method can be used as a safe and healthy intervention for the treatment of liver diseases such as NASH and NAFLD.

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Ethical statement

This study was conducted under the ethics approval code issued by the Golestan University of Medical Sciences (ID: IR.GOUMS.REC.1401.005).

Conflicts of interest

There is no conflict of interest to be declared by the authors.

Author contributions

This article is derived from a thesis approved by the University of Aliabad. The authors are sincerely grateful for the cooperation extended during this study.

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