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The role of eight weeks of combined high-intensity interval training in modulating intrahepatic FNDC5 protein and irisin levels in male rats with non-alcoholic steatohepatitis

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Abstract

Background: Non-alcoholic steatohepatitis (NASH) is one of the prevalent metabolic diseases, and knowing its treatment methods is very important. This study investigates the effect of eight weeks of combined high-intensity interval training on intrahepatic FNDC5 protein and irisin in male rats with non-alcoholic steatohepatitis.

Methods: In this study, 40 rats aged 6 to 8 weeks were divided into two groups: healthy (n=20) and high-fat diet (HFD) (n=20). After eight weeks and assurance of disease induction, the HFD group was randomly divided into control-patient (n=9) and training-patient (n=9). Also, the healthy group was divided into control-healthy (n=9) and training-healthy (n=9). The training group rats performed HIIT in aquatic and land environments (Saturdays and Wednesdays in aquatic environments and Mondays on a treadmill). Western blot method was used to measure FNDC5 and irisin proteins, and the spectrophotometric method was used to measure liver enzymes (ALT and AST). One-way ANOVA and Bonferroni's post hoc test ($P<0.05$) were used to determine the difference between groups.

Results: After eight weeks of combined high-intensity interval training, there was no significant difference in intrahepatic FNDC5 protein levels between the groups ($P=0.125$). Intrahepatic irisin protein levels significantly increased in the training-healthy group compared to the control-healthy group ($P=0.046$). Additionally, there was a significant increase in the training-patient group compared to the control-patient group ($P=0.036$) and a significant increase in the training-healthy group compared to the control-patient group ($P=0.011$).

Conclusion: In general, combined high-intensity interval training (aquatic + land) can increase intrahepatic irisin. Thus, this type of training can be considered one of the potential non-pharmacological options for treating NAS. However, more research is needed to reach definitive results.

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FNDC5 protein, rat
Lipid metabolism
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Article Type: Original Article

Highlights

What is current knowledge?

Currently, the optimal exercise protocol to improve non-alcoholic steatohepatitis is still under discussion despite the proven benefits of exercise in treating fatty liver disease.

What is new here?

A new protocol of high-intensity intermittent exercise combining water and a treadmill has been presented. It has shown positive effects on the lipid metabolism mechanism in the liver of non-alcoholic steatohepatitis patients without caloric restriction.

Introduction

Nonalcoholic steatohepatitis (NASH) affects up to 30% of people with NAFLD and is characterized by inflammation, necrosis of the liver, severe insulin resistance, and cardiometabolic dysfunction. With disease progression mainly due to insulin resistance, NASH affects up to 37% of people with type 2 diabetes (T2DM). NASH is strongly associated with cardiovascular disease morbidity and mortality and the risk of liver cirrhosis. It increases hepatocellular carcinoma and a wide range of extrahepatic malignancies (1). Management of NASH focuses on lifestyle modification regarding diet quality and increased physical activity to reduce body mass by 7–10% (2).

Irisin originates from cleavage of the extracellular portion of fibronectin type III domain-containing protein 5 (FNDC5) and was first identified as a myokine regulated by exercise. By promoting white fat cell "browning" and thermogenesis, secreted irisin increases energy expenditure (3), which in turn can limit body weight gain and insulin resistance and plays an important role in diabetes and non-alcoholic fatty liver diseases (NAFLDs), including non-alcoholic steatohepatitis (NASH) (4,5). Furthermore, the relationship between systemic irisin levels and the development of NAFLDs and nonalcoholic steatohepatitis is still debated (6).

Even though adipose tissues and the liver also express and secrete irisin, it is difficult to estimate the relative contribution of muscle, liver, and adipose tissue to the secretion of circulating irisin. Furthermore, the relationship between systemic irisin levels and the development of NAFLDs and nonalcoholic steatohepatitis is still debated (7). Wrann et al. (2015) have shown that 32 days of voluntary exercise on a turning wheel in six-week-old male rats leads to an increase in the expression of the FNDC5 gene (7). Bonfante et al. (2017) showed that combined training maintained FNDC5/irisin levels and provided metabolic and fitness benefits in obese men (8). Also, Makiel et al. (2023) showed that combined exercise improved irisin performance, reduced insulin resistance, and reduced visceral fat mass in men with metabolic syndrome (9). There is evidence that exercise-induced FNDC5 triggers the effect of exercise through skeletal muscle on other organs, including visceral fat (10,11). Through irisin, FNDC5 can indirectly convert white fat into brown fat, and with this mechanism, reduce obesity and diabetes and improve NAFLD. Reisi et al. (2016) concluded that resistance exercise may improve body composition by increasing thermogenesis in white adipose tissue through irisin secretion (11).

As a result, it is possible that the levels of FNDC5 and exercise determine the amount of brown fat in the body. Therefore, there is a hypothesis that brown adipose tissue (BAT) can improve insulin sensitivity and cause weight loss (12). Bonfante et al. (2017) showed that higher levels of FNDC5/irisin in obese middle-aged men were associated with a better metabolic profile and lower risk of type 2 diabetes (12).

High-intensity interval training (HIIT) consists of periods of high-intensity exercise followed by periods of passive or active recovery (13). Emerging longitudinal evidence from small clinical trials suggests that HIIT produces comparable reductions in liver fat to traditional moderate-intensity continuous exercise (14). However, these studies did not include subjects with biopsy-proven NASH (15). Since water has a high-temperature transfer property and can cause the body temperature to decrease during sports activities and thus reduce the systemic inflammation of the body (16), it is likely that the increase in lipid metabolism and its related factors, including irisin, increases in combination with training in the land. Despite this, there is little research in this regard, and the minimum necessary amount of physical activity for developing physical health is still not completely clear (16). the present study investigated the effect of eight weeks of combined high-intensity interval training on intrahepatic FNDC5 protein and irisin in male rats with non-alcoholic steatohepatitis.

Methods

This research selected 40 male Sprague-Dawley rats (age: 8 weeks) with an average weight of 230 ± 20 grams. The rats were kept in the animal house of Shiraz University with an ambient temperature of 22-24°C, humidity of 45%, and a light-dark cycle of 12-12. The ethical principles of working with the animals in the study were considered per the Helsinki Declaration, and the code of ethics

obtained was IR.SUMS.AEC.1402.017. The rats were divided into standard food (n=20) and high-fat diet (HFD) groups. HFD was given to rats in the form of emulsion by gavage method (10 ml/kg/day). The content of HFD consisted of 77% fat (corn oil and cholesterol powder), 14% protein (milk powder), and 9% carbohydrates (sucrose) (17). The healthy group was also gavage with the same amount of salt solution (saline) daily. After proving the induction of disease in rats, the high-fat diet group was randomly divided into control-patient (n=9), exercise-patient (n=9) and healthy group and control-healthy (n=9), group exercise-healthy (n = 9) were divided. The HFD of the patient groups continued until the end of the training period.

HIIT swimming workout:

In the first week of acclimatization, the rats swam alternately in the animal pool (diameter 160 cm and height 80 cm) with a water depth of 50 cm and an average temperature of 30±0.5°C for 20 minutes. In the second week of adaptation, to familiarize themselves with the type of interval training, they were taken out of the water several times after swimming for one minute by the resting plate and put back in the water (18). Forty-eight hours after the last familiarization session, the main exercise was performed for eight weeks, two days a week (Saturday and Wednesday), according to Table 1 (19).

Table 1. HIIT swimming workout protocol (Saturday and Wednesday)

Week	Number (Interval)	Attempt duration (Seconds)	Rest period (Seconds)	Amount of overload (Percentage of body weight)
Week one	20	30	30	7
Week two	20	30	30	8
Week three	20	30	30	9
Week four	20	30	30	10
Week five	20	30	30	11
Week six	20	30	30	12
Week seven	20	30	30	13
Week eight	20	30	30	14

HIIT on a treadmill:

Two weeks before the start of the study, the animals were acclimatized through a daily low-intensity running protocol for 20 minutes on a treadmill at a speed of 10 m/min. After the familiarization phase, the main exercise protocol, according to Table 2, was performed one day a week (Mondays) and for eight weeks (20,21).

Table 2. Land training protocol

Week	Duration of main training (min/day)	Vo2max (Percentage of intensity)	No. of sessions per week	Incline
1	20	10 m/min (2 min. recovery) 16 m/min (3 min. training)	1	0˚, 60%Vo_{2max}
2	20	16 m/min (2 min. recovery) 23 m/min. (3 min. training)	1	0˚, 70%Vo_{2max}
3	20	22 m/min (2 min. recovery) 30 m/min (3 min. training)	1	0˚, 80%Vo_{2max}
4	20	22 m/min (2 min. recovery) 30 m/min (3 min. training)	1	0˚, 80%Vo_{2max}
5-8	20	28 m/min (2 min. recovery) 37 m/min (3 min. training)	1	0˚, 90%Vo_{2max}

Forty-eight hours after the last training session, rats were injected intraperitoneally with a combination of ketamine (30 to 50 mg/kg body weight) and xylazine (3 to 5 mg/kg body weight) and were anesthetized and dissected, and the liver tissue was harvested. To measure irisin proteins (β-Actin (C4): sc-47778, Irisin (42-112) (Human, Rat, Mouse, Canine) - purified IgG antibody) catalog number G-067-17 and FNDC5 (β-Actin (C4): sc-47778, Anti-FNDC5 antibody ab131390) was done through western blot technique.

Western Blot

In general, the steps of the western blot technique include tissue lysing, determination of protein concentration by Bradford, preparation of different concentrations of BSA to draw a standard curve, protein concentrations, water and sample buffer, sample preparation, and electrofuge on SDS gel. page, preparation of solutions, test method and making of lower and upper gel, electrophoresis on SDS page gel, western blot or immunoblotting, transfer step from gel to paper, blocking step, incubation step with primary antibody (β-Actin (C4) : sc-47778, Irisin (42-112) (Human, Rat, Mouse, Canine) - purified IgG antibody) catalog number G-067-17 and (β-Actin (C4): sc-47778, Anti-FNDC5 antibody ab131390) from abcam company, incubation step with secondary antibody (m-IgGκ BP-HRP: sc-516102, mouse αanti-rαββit IgG-HRP: sc-2357), detection step, film development step in the dark-room, method It was striping.

Data analysis

One-way variance was used to analyze the data, and if the differences were significant, Bonferroni's post hoc test was used to determine the exact location of the differences. The statistical analysis was carried out using the SPSS version 26 software, and the significance level was set at P<0.05.

Results

Results related to proof of disease and weight changes

Figure 1 shows the mean ± standard deviation of the weight changes of the healthy (n = 20) and high-fat diet (HFD) (n = 20) groups during eight weeks of high-fat diet induction. In order to prove the development of NASH disease, two rats were randomly sacrificed from the diseased (n=2) and healthy (n=2) groups. As an example, in Figure 2, the diseased liver and the healthy liver are demonstrated together for comparison. In Figure 3, the results of Oil red O staining of diseased and healthy liver tissue are compared and reported. Table 3 of patient samples 1 and 2 after eight weeks of feeding with a high-fat diet, steatosis and inflammation score, serum ALT and AST values, and liver histological analysis showed that the liver of rats was in the second stage of fibrosis. Based on the average weight of each group in the entire period of exercise intervention (Figure 4), it was found that between exercise-patient and exercise-healthy groups (P=0.038) and control-patient (P=0.027) and control-healthy (P=0.031) there was a significant difference in the seventh week. Therefore, the average weight of the exercise-patient group experienced a significant decrease compared to the control-patient group (P=0.027).

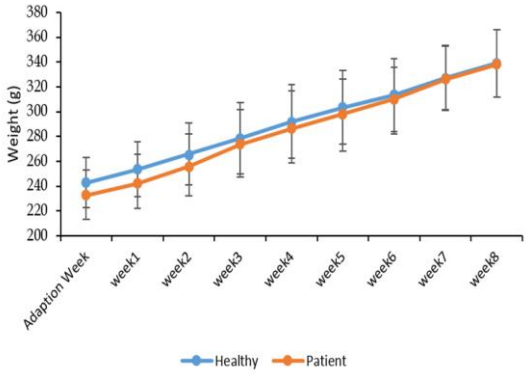

Figure 1. Mean ± standard deviation of the weight changes of the healthy (n = 20) HFD groups in the first eight weeks of fatty liver induction.

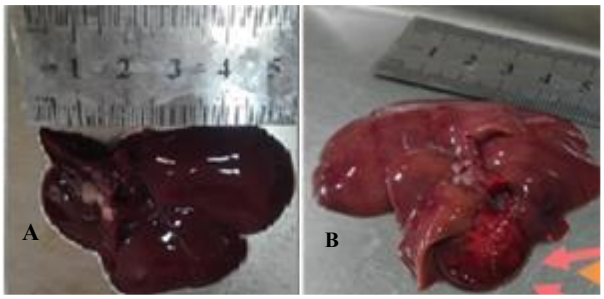

Figure 2. Comparison of the appearance of healthy liver (A) and fatty liver (B), immediately after killing in the diseased and healthy groups

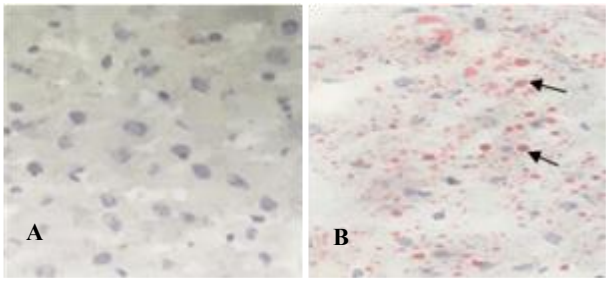

Figure 3. Staining of liver tissue by Oil red O, A: Healthy liver—not taking on any red color due to the absence of fat. B: Fatty liver, lipids are red.

Table 3. Results of tissue and blood tests to show non-alcoholic steatohepatitis (NASH).

Rat No.	Steatosis grade	Inflammation grade	Fibrosis stage	ALT	AST
1 (Patient)*	2.33	0.3	2	64.54	60.9
2 (Patient)*	2.75	0.9	2	69.7	67.84
1 (Healthy)*	0	0	0	46.3	41.21
2 (Healthy)*	0	0	0	40.39	38.41

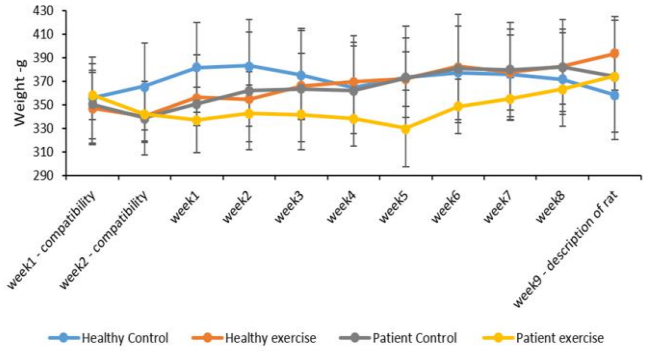

Figure 4. Mean ± standard deviation of the weight changes of the four experimental groups in the second eight weeks following the emergence of non-alcoholic steatohepatitis (NASH) (initially, two weeks were considered for the rats' adaptation to the training environment, and then the main training was performed from weeks one to eight according to the protocol. The ninth week was the week for rats' dissection.

Western Blot results

In Table 4, descriptive data, including the mean, standard deviation, minimum, maximum, and the number of animals for each dependent variable in terms of experimental groups, are displayed.

Table 4. Descriptive statistics of the research variables

Variable	Group	Mean	SD	n
FNDC5 (pg/ml)	Control-healthy	1	0	2
	Training-healthy	1.035	0.106	2
	Control-patient	0.695	0.346	2
	Training-patient	0.39	0.268	2
Irisin (pg/ml)	Control-healthy	1	0	2
	Training-healthy	2.582	0.62	2
	Control-patient	0.235	0.035	2
	Training-patient	1.924	0.138	2

In Figure 5, the results of the western blot bands for intrahepatic FNDC5 protein are reported for each group. As shown in Figure 6, based on the results of the one-way analysis of the variance test, there was no significant difference between the mean of FNDC5 (P=0.125). However, after examining the averages, it was found that the training-patient group had a non-significant decrease of 43.884% compared to the control-patient group (P=0.9).

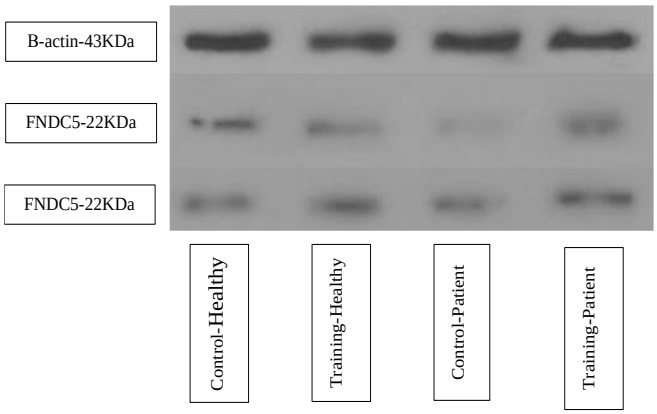

Figure 5. Results of the Western blot for intrahepatic FNDC5 protein; the concentration of this protein is determined according to its bandwidth and color intensity compared to beta-actin in the liver.

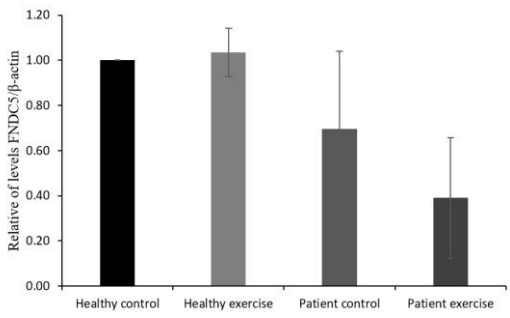

Figure 6. Intrahepatic FNDC5 protein levels- no significant difference between the research groups (P=0.125)

In Figure 7, the results of the western blot bands for intrahepatic irisin protein are reported for each group. As shown in Figure 8, based on the results of one-way variance analysis, there is a significant difference between the irisin mean (P=0.007). According to Bonferroni's post hoc test, this difference was associated with a significant increase in the training-healthy group compared to the control-healthy (P=0.046) and control-patient (P=0.011) groups, and there was a significant increase in the training-patient group compared to the control-patient group (P=0.036).

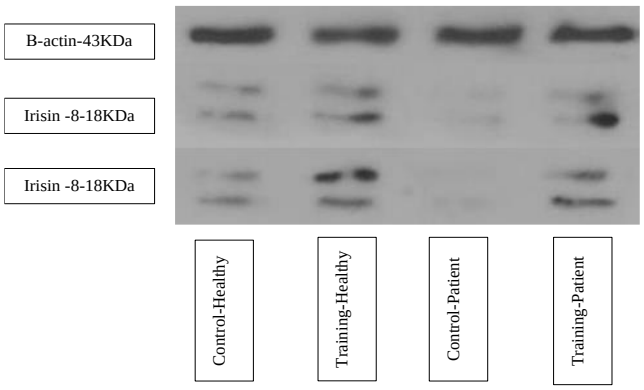

Figure 7. Results of the Western blot for intrahepatic irisin protein

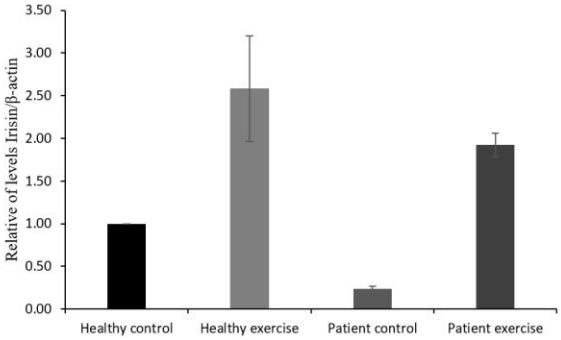

Figure 8. Intrahepatic irisin protein levels- *: significant increase in the training-healthy group compared to the control-healthy (P=0.046) and control-patient (P=0.011), #: significant increase in the training-patient group compared to the control-patient (P=0.036).

Discussion

The present study aimed to investigate the effect of eight weeks of high-intensity interval training on intrahepatic FNDC5 and irisin protein in male rats with non-alcoholic steatohepatitis. The findings showed that there was a non-significant decrease in FNDC5 protein in the training-patient group compared to the control-patient group. Also, there was a significant increase in irisin protein in the training-patient group compared to the control-patient group and a significant increase in the training-healthy group compared to the control-patient group. Based on the results of recent research, it is worth mentioning the study conducted by Bastu et al. (2018). They found that after eight weeks of aerobic training, there was a significant increase in the irisin variable in the training group compared to the control group (22). Another relevant study is that of Dehghani et al. (2022). Following a period of resistance training in their research, these researchers found a significant increase in plasma irisin levels and no difference in FNDC5 levels in men aged 30 to 50 years compared to the control group (23). The study by Kurdiova et al. (2014) found that while muscle FNDC5 mRNA increased in pre-diabetic conditions, it did not increase in type 2 diabetes or advanced insulin resistance. They also found that FNDC5 in adipose tissue and irisin in plasma decreased in type 2 diabetes. Further, they stated in their research that circulating irisin was positively related to muscle mass, strength, and metabolism and negatively related to fasting blood sugar (24). First, it should be said that according to the previous findings and the current research findings, FNDC5 is the precursor of irisin, and their changes are expected to be aligned. However, in response to different conditions (either type of disease, type of intervention or type of subject) they showed different changes. The researchers simultaneously investigated the adaptations and changes of two proteins, FNDC5, and irisin, in liver tissue in response to a high-fat diet and high-intensity interval training interventions. Part of the research findings of Cordiva et al. (2014) were consistent with the findings of the present research. In the current research, combined high-intensity interval training did not have a significant effect on FNDC5 levels in the groups. Based on the findings of Kurdiova et al., FNDC5 may elicit varying responses to physical activity depending on the disease model and tissue being measured.

However, the findings of Kurdiova et al.'s research were partially inconsistent with the findings of the present study. In the present study, irisin increased significantly in the training groups compared to the control group, and this shows that the sports-induced adaptation increases the breakdown of inactive FNDC5 and turns it into active irisin. Also, the FNDC5/Irisin/UCP-1 signal increases and augments fat browning. As a result, it can be suggested that contrary to the results of Kurdiova et al., the findings of this research indicate that combined high-intensity interval training can have a potential effect on the browning of white fat in the liver and improve non-alcoholic steatohepatitis (NASH) (24).

There is evidence that irisin has a positive correlation with muscle mass and a negative correlation with fat mass (25). In this regard, in the present study, the weight of the training-patient group had a significant decrease compared to the control-patient group, wherein the weight loss was caused by the reduction of visceral fat in the training-patient group because both groups constantly used a 77% high-fat diet. This decrease in fat levels occurred while the intrahepatic irisin levels, as an indicator of blood serum irisin levels, increased significantly in the training-patient group compared to the control-patient. In a study by Jiang et al. (2021), mice overexpressed irisin had a slight weight loss compared to the control group. Muscle mass is the only predictor of serum irisin levels (26).

In the present study, the weight difference in the training-patient group was significantly lower compared to the control-patient rats. Therefore, it is likely that combined high-intensity interval training reduced fat and increased muscle mass in the training-patient group compared to the control-patient rats.

Short-term control of obesity through weight loss exercise may improve insulin resistance by increasing irisin levels, even in rats with a high-fat diet (22), as in the present research, in which rats in the patient groups (either control-patient or training-patient) were constantly using a high-fat diet.

Based on these results, it can be proposed that following high-intensity interval training, the rate of FNDC5 conversion to irisin increased, and subsequently, the activity of irisin increased.

Since irisin is an indicator of fat browning, it is possible that as irisin increases, the hepatic and visceral fat also decrease. Accordingly, in the present study, a significant decrease in the weight of the training-patient group compared to the control-patient group was observed.

Conclusion

Since irisin has a muscle source, it is possible that with weight loss in the training-patient group, the muscle volume increased following combined high-intensity interval training. Also, part of the increase in hepatic irisin can be attributed to the augmented release of muscle irisin and its positive feedback effect on the hepatic irisin increase in non-alcoholic steatohepatitis (NASH) disease. Nonetheless, further research is necessary to obtain conclusive results.

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Ethical statement

The ethical principles (Code of ethics) of the study were considered in accordance with the principles of working with laboratory animals approved by Shiraz University of Medical Sciences (IR.SUMS.AEC.1402.017).

Conflicts of interest

The writers of this piece want to clarify that they have no conflicts of interest.

Author contributions

All authors contributed to the present study.

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