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ORIGINAL ARTICLE

The Effect of Eight Weeks of High-Intensity Interval Training on Plasma LRP1, AB1-42, and Insulin Resistance in Obese Elderly Diabetic Rats

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ABSTRACT

Background. Aging is a complex and multifaceted process leading to a widespread decline in nerve function. In addition to causing weakness in the elderly, neurological disorders in old age are also effective in the development of chronic diseases. **Objectives.** Therefore, this study aims to investigate the effect of eight weeks of HIIT exercises on LRP1, AB1-42, and insulin resistance in obese elderly diabetic rats. **Methods.** Twenty-four rats (20 months old) were bred, 16 diabetic rats were randomly divided into two diabetic control groups (SHAM) and diabetic exercise (HIIT), and the remaining eight rats were in the healthy control group (CON). After making sure that the rats became diabetic, they were familiarized with the treadmill for a week, and the maximum speed test was performed to calculate the training intensity for the training group. Then, the rats in the HIIT group ran five sessions every week for 8 weeks on a treadmill with a Vo2max intensity of 90% in 30-second intervals. The incline of the treadmill was zero in all training sessions. The training started in the first week with 5 30-second moves for each session, and one move was added every week so that it reached 12 moves by the eighth week. In all weeks, the rats rested for one minute between intervals (continuing the treadmill at 7.8 m/min, equivalent to 30% of the maximum speed). **Results.** After eight weeks of HIIT exercises, a significant difference was observed between the AB1-42 index of the groups (P=0.001). The results of the follow-up test showed that there was a significant difference between AB1-42 of the exercise group with the diabetic control group, the healthy control group, and the diabetic control group with the healthy control group (P=0.001, P=0.001, and P=0.001, respectively). A significant difference was observed between LRP1 groups (P=0.001). The follow-up test results showed a significant difference between the LRP1 of the exercise group and the diabetic control group and the healthy control group and the diabetic control group (P=0.001 and P=0.001, respectively). Also, after eight weeks of training, there was a significant change in weight, glucose, insulin, and insulin resistance indices (P=0.001, P=0.001, and P=0.001, respectively). **Conclusion.** It is suggested that by participating in HIIT exercises, the elderly can reduce the process of nerve tissue damage and the progress of diseases such as diabetes.

KEYWORDS: ***Diabetes, HIIT, High-Intensity Interval Training, LRP1, AB1-42, Obese Elderly, Diabetic Rats.***

INTRODUCTION

In people with obesity, Insulin resistance, defined as a reduced tissue sensitivity to insulin, is associated with significant health risks such as excess weight, high blood pressure, dyslipidemia,

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cardiovascular diseases, and type 2 diabetes (1-6). Diabetes is a metabolic disorder characterized by elevated blood glucose levels, leading to various pathological changes such as neuropathy, nephropathy, immune system impairment, vascular damage, and impaired tissue regeneration (7-11). Recent studies suggest that obesity leads to neuronal apoptosis and cognitive impairment by increasing inflammation and oxidative stress and that chronic disturbances in glucose homeostasis, impaired insulin signaling, and hypometabolism are closely related to cognitive impairment and the pathology of neurological diseases (2, 12, 13). Genetic disruption of low-density lipoprotein receptor-related protein 1 (LRP1) in the central nervous system or selectively in inhibitory gamma-aminobutyric acid (GABA)ergic neurons results in increased food intake, decreased energy expenditure, and metabolic changes leading to obesity. In addition to its critical role in metabolism, LRP1 is a major regulator of neurotransmission, synaptic plasticity, and amyloid-β (Aβ) clearance (14). In a study by da Cruz Rodrigues and colleagues (2024), it was shown that in mice lacking LRP1 in GABAergic neurons, serum levels of ApoJ were increased. Since LRP1 is a potential receptor for ApoJ and serum ApoJ levels are elevated in individuals with obesity and type 2 diabetes and diet-induced obese mice, this may indicate a connection (14). Therefore, the neurological dysfunction resulting from the loss of LRP1 in GABAergic neurons may play a role in motor abnormalities, with energy imbalance and obesity linked to cognitive deficits such as impaired memory and learning (15). Also, the biology of Amyloid Precursor Protein (APP) may play a significant role in linking obesity to cognitive decline (16). Ab1-42, in the form of amyloid fibrils, causes neuronal dystrophy, free radical production, and pro-oxidative damage in diabetics (17). T2DM is strongly associated with cognitive impairment due to failure in the action of glucose absorption in the neurons for energy production. T2DM and Alzheimer's disease are both interlinked with insulin resistance, insulin growth factor (IGF) signaling, inflammatory response, oxidative stress, glycogen synthase kinase 3β (GSK3β) signaling mechanism, amyloid beta (Aβ) formation from amyloid precursor protein (APP), neurofibrillary tangle formation, and acetylcholine esterase activity regulation. Because of shared mechanisms among Type-1 Diabetes (T1DM), T2DM, and Alzheimer's disease, researchers termed "Type-3 Diabetes" (18).

According to the World Health Organization, the global diabetes population is approximately 463 million people and is projected to exceed half a billion by 2030 (8). There is no specific cure for diabetes, but the control and management methods are advancing. The effect of exercise and physical activity on one of the latest factors involved, LRP1, plasma AB1-42 levels, and insulin resistance, is one of the therapeutic strategies (14, 19). Exercise training, especially high-intensity interval training (HIIT), benefits brain health and cognitive function and reduces the detrimental effects of neurological diseases such as Alzheimer's, diabetes, Parkinson's, and depression (2, 12, 13, 20). One of the essential elements that induces the beneficial effects of exercise on the brain is the reduction of amyloid load. However, the impact of exercise on brain and blood Aβ levels is not well understood (21). Studies on changes in amyloid load and factors involved in Aβ and sLRP1 clearance following exercise have contradictory results. Therefore, this study aimed to investigate the effects of eight weeks of HIIT on plasma LRP1, AB1-42 levels, and insulin resistance in obese and diabetic rats.

MATERIALS AND METHODS

Study Design and Participants. This study was an experimental design with a post-test, including two control groups. Twenty-four male Wistar rats, aged 20 months and weighing 503.27 ± 36.5 g, were obtained from the animal laboratory at Shahid Sadoughi University of Medical Sciences, Yazd, Iran. The rats were housed under standard conditions (temperature: 20±2°C, humidity: 50±10%, and a 12-hour light/dark cycle) and allowed to acclimatize for one week. After acclimatization, the rats were randomly assigned into three groups of eight. Two of these groups were induced to develop diabetes. This was achieved by administering a single intraperitoneal injection of STZ (Sigma, Germany) after a 12-hour fasting period. The STZ was dissolved in a sodium citrate buffer solution (pH 4.5) and injected at 40 mg/kg of body weight. Five days later, blood glucose levels were measured, and rats with glucose levels above 300 mg/dL were classified as diabetic. Blood glucose levels were assessed using samples from the rats' tails and

measured with a glucometer (Beurer Model GL42, Germany) using the glucose oxidase enzymatic method. A blood glucose level exceeding 300 mg/dL was used as the criterion for diagnosing diabetes.

After inducing diabetes, 16 diabetic rats were randomly assigned to either a diabetic control group (SHAM) or a training group (HIIT), while the remaining eight rats made up the healthy control group (CON). All rats were given the same diet throughout the study (both before and after exercise), with unrestricted access to food and water to assess the direct effects of training and eliminate any confounding factors related to food intake reduction and its influence on the measured parameters (Figure 1). Body weight was measured weekly using a Rat Grimace Scale, with a precision of 0.0001.

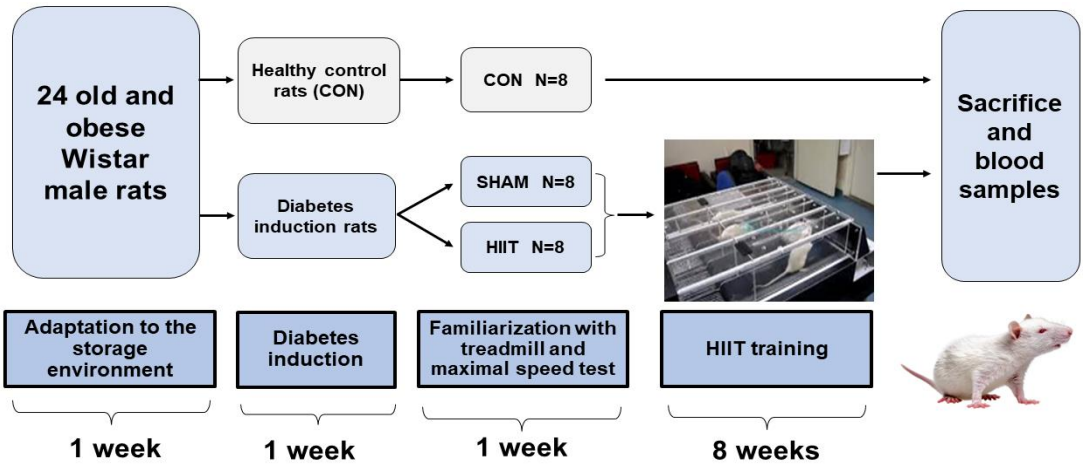

Figure 1. Flowchart of the study.

Exercise training protocol. Once diabetes was confirmed in the rats, a one-week familiarization period with the treadmill was conducted, including a maximum speed test to determine the exercise intensity for the training group. The HIIT group underwent treadmill running for 8 weeks, with 5 sessions per week, at an intensity of 90% of their VO2max, in 30-second intervals. The treadmill's incline was kept at zero during all sessions. The training began in the first week with 5 intervals of 30 seconds per session, and each week, one additional interval was added, reaching 12 intervals by the eighth week. Between each interval, the rats rested actively for one minute (walking at 7.8 meters per minute, or 30% of their maximum speed). Each session started and ended with a warm-up and cool-down phase: the warm-up was done at 40-50% of maximum speed (8.11-8.14 m/min), and the cool-down at 20-30% of maximum speed (7.8-9.5 m/min), with both lasting for 5 minutes. The rats' maximum speed was determined based on VO2max, which averaged 29.41 ± 12.3 meters per minute. The exercise intensity was set at 90% of this value (1.26 m/min). The living conditions of the control group rats were the same as those of the exercise group, except for the daily exercise sessions.

Measurements. Analyses of blood sampling. Blood samples were collected 24 hours after the last training session, following an 8-hour fasting period to eliminate the acute effects of exercise training and any uncontrolled stress factors during the training program. The rats were euthanized under anesthesia using ketamine (90 mg/kg) and xylazine (10 mg/kg). After confirming that the rats were fully anesthetized, their chest cavities were opened, and blood was directly drawn from the heart to minimize distress. Plasma was then separated from the blood using a centrifuge (10 minutes at 3000 g). All procedures followed the United States Public Health Service guidelines for treating and using laboratory animals. Plasma LRP1 levels were measured using an animal-specific ELISA kit (antibodies-online, USA), while AB1-42 plasma levels were measured using the CSB-E10786r kit from Cusabio Biotech (China), also via ELISA. Insulin levels were assessed using a sandwich and competitive enzyme immunoassay. Glucose was measured using a biochemical kit using the glucose oxidase enzymatic method. Finally, insulin resistance was evaluated using the Homeostasis Model

Assessment of Insulin Resistance (HOMA-IR), calculated by multiplying glucose concentration by insulin concentration and dividing by a constant of 22.5.

Statistics analysis. Descriptive statistics, including the mean and SD, were used to summarize the data. The normality of the data was assessed using the Shapiro-Wilk test, and the homogeneity of variances was tested with Levene's test. One-way ANOVA was performed to determine whether there were significant differences in the means of the variables across the groups, followed by Tukey's post hoc test. The data were analyzed using SPSS version 23, and a significance level of $P < 0.05$ was considered for all tests.

RESULTS

As shown in Table 1, after eight weeks of exercise training, the body weight of obese rats significantly decreased in the training group (HIIT) compared to both the healthy control (CON) and diabetic control groups (SHAM) ($P = 0.001$). Concerning blood glucose levels, a significant difference was observed between the groups after eight weeks of HIIT ($P = 0.001$). Post hoc analysis revealed that glucose levels in the training group were significantly lower than in SHAM ($P = 0.001$). Significant differences were also observed between the CON, HIIT, and SHAM ($P = 0.001$). Further results indicated significant differences in insulin levels across the groups ($P = 0.001$). Insulin levels in CON were higher compared to both SHAM and HIIT. After eight weeks of training, insulin levels in HIIT were significantly higher than those in SHAM ($P = 0.001$). Moreover, significant differences in insulin levels were found between CON and both HIIT and SHAM ($P = 0.001$ for both).

Table 1. Results of one-way ANOVA test on weight, glucose, insulin, and HOMA-IR of groups

Variables	Groups			F	P
	SHAM	CON	HIIT		
Weight pre-training (g)	4.17±503.46	4.07±503.41	7.73±502.96	-	-
Weight post-training (g)	5.75±567.97	4.14±565.19	5.68±482.38	688.15	0.0001*
Glucose (mg/dl)	31.32±371.73	7.50±91.65	17.43±202.05	356.07	0.0001*
Insulin (µIU/mL)	0.17±5.19	1.53±13.74	0.10±7.30	200.20	0.0001*
HOMA-IR	0.47±4.76	0.45±3.11	0.30±3.64	32.53	0.0001*

* : P < 0. 05

Regarding the insulin resistance index, significant differences were observed between the groups after eight weeks of HIIT ($P = 0.001$). Post hoc testing showed that insulin resistance in HIIT was significantly lower than in SHAM ($P = 0.001$), and significant differences were also found between CON and HIIT and SHAM ($P = 0.001$ for both). The study revealed significant differences in AB1-42 levels among the groups after eight weeks of training ($P = 0.001$) (Table 2). Figure 1 indicates significant differences between HIIT and SHAM, as well as between CON and SHAM ($P = 0.001$ for both). A significant difference was also observed between CON and HIIT ($P = 0.006$).

Table 2. Results of one-way ANOVA test on AB1-42 and LRP1 of groups

Variables	Groups			F	P
	SHAM	CON	HIIT		
AB1-42 (Pg/mL)	0.13±0.803	0.07±0.543	0.08±0.485	24.91	0.0001*
LRP1 (µg/mL)	1.37±8.97	0.45±4.91	0.21±4.21	74.36	0.0001*

* : P < 0. 05

Furthermore, the study showed significant differences in LRP1 levels among the groups after eight weeks of HIIT ($P = 0.001$). As shown in Figure 2, significant differences were found between HIIT and both SHAM and CON ($P = 0.001$ for both). However, no significant difference was noted between CON and HIIT ($P = 0.21$).

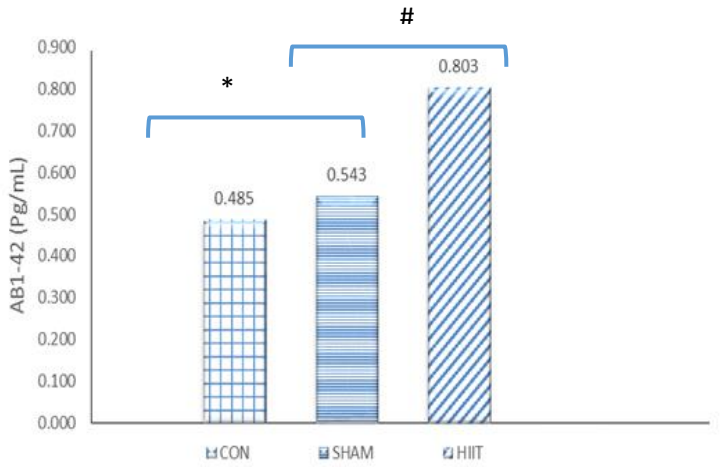

Figure 1. Average plasma levels of Aβ1-42 in the study groups.
***:** significant difference between CON and SHAM. **#:** significant difference between SHAM and the HIIT

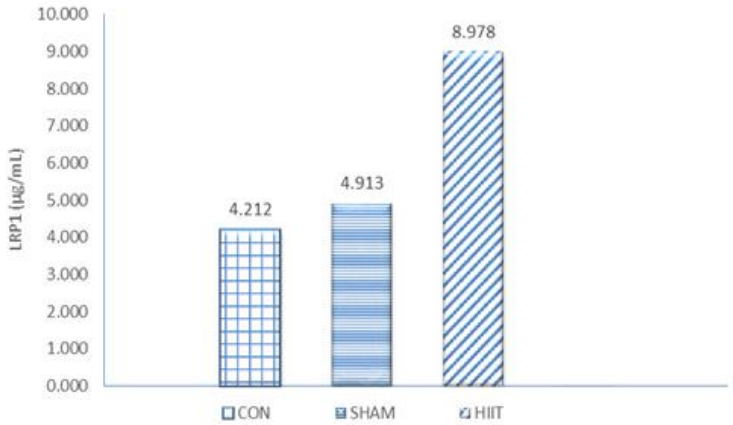

Figure 2. Average plasma levels of LRP1 in the study groups.
***:** significant difference between CON and SHAM. **#:** significant difference between SHAM and HIIT.

DISCUSSION

The present study showed plasma glucose levels, weight, and insulin resistance were lower in HIIT than in SHAM and CON. Weight gain and subsequent impaired glucose metabolism and IR in the hippocampus of diabetic rats can be closely related to cognitive impairment, inefficient glucose metabolism, and metabolic stress in the brain, which may impair cognitive-motor function and contribute to the destruction of the insulin receptor system (22). In this regard, Tayebi et al. (2024) observed that eight weeks of HIIT swimming training significantly reduced insulin resistance and fasting blood sugar (FBS) in diabetic rats (2). In another study, Shamshadi et al. (2023) showed that eight weeks of HIIT training significantly reduced blood glucose levels and insulin resistance while significantly increasing blood insulin levels in elderly diabetic rats (23). HIIT training induces several metabolic adaptations, such as enhanced oxygen uptake, increased muscle mitochondrial content, more excellent fatty acid transporter proteins in muscle tissue, and improvements in mitochondrial enzymes and β-oxidation (2, 12, 13, 20).

Additionally, HIIT leads to other changes, including increased skeletal muscle oxidative capacity, alterations in carbohydrate metabolism, higher resting glycogen content, and increased levels of GLUT4 and glycolytic enzymes. Muscle contractions, which occur during HIIT, mimic the effects of insulin. They promote an increase in GLUT4 proteins and enhance the cell membrane's permeability to glucose, which helps lower blood glucose levels in people with diabetes (24). In another study, Oh and Lee (2023) showed that a

combined resistance and aerobic training program (at 50% and 80% VO2max intensity) led to a significant reduction in body weight but did not have a meaningful impact on blood glucose levels in middle-aged obese women (25). Similarly, Suh et al. (2011) reported reduced insulin resistance following exercise training (26). Differences in the type of exercise training, intensity, baseline blood glucose levels, and sample characteristics could explain the variation in results across studies.

Additionally, Safarnezhad et al. (2020) found that although eight weeks of HIIT reduced blood glucose levels and insulin resistance, the training group had no significant weight loss (27). Compared to the current research, this study's lack of weight reduction was attributed to using a high-fat diet throughout the study period. Exercise training results in a range of positive benefits for neurobiological outcomes in animal and human diabetic studies, such as increased insulin-like growth factor 1 (IGF-1), increased brain-derived neurotrophic factor, neurogenesis, functional plasticity, decreased inflammatory cytokines, decreased cortisol response to stressors, and improved cognitive function. Specifically, training can increase IGF-1 levels, which may lead to improved neurogenesis and vessel remodeling in the brain (28).

The findings of this study also showed that plasma levels of LRP1 and AB1-42 were lower in HIIT compared to SHAM and CON. However, HIIT exercise training successfully lowered the levels of these neurotoxic factors compared to the other two groups. In a study, Tayebi et al. showed that exercise training improves cognitive function by increasing neurogenesis, reducing the loss of dopaminergic neurons, increasing cerebral blood flow, increasing antioxidant capacity, and improving autophagy (2, 12, 13, 20, 29, 30). In this regard, a study by Falah Mohammadi and Ebrahimzadeh (2013) found that 6 weeks of combined running on a rotating wheel reduced Aβ1-42 levels in diabetic male rats (31). Various studies have proposed different mechanisms through which exercise may reduce Aβ levels. Voluntary exercise might influence the metabolism of amyloid precursor protein and the Aβ cascade, thus reducing the production of Aβ (31). Exercise training likely lowers Aβ1-42 levels in the brain by promoting the degradation and clearance of Aβ (32). The main finding of this study is that HIIT training managed to lower Aβ1-42 protein levels in the blood of diabetic rats, suggesting that HIIT can have a beneficial impact on one of the complications associated with diabetes. Khoramshahi et al. (2023) found that eight weeks of voluntary exercise training in an enriched environment decreased Aβ levels in the hippocampus of rats with type 2 diabetes (33). Based on the findings of this research, it can be concluded that exercise training positively affects Aβ signaling pathways, reduces insulin resistance and blood glucose levels, and improves hyperglycemia, leading to a reduction in cellular damage and neuronal death in the hippocampus. The deposition of the Aβ1-42 protein is therefore considered a key pathological factor in type 2 diabetes (33). Similarly, Zarrin Afzal et al. (2020) demonstrated that three weeks of moderate-intensity interval training brought about significant changes in the levels of LRP1 and Aβ in the plasma of Alzheimer's disease rats (19).

However, the exact mechanism responsible for the positive effects of exercise on brain function in diabetics is still not well understood. One possible mechanism for the protective ability of exercise could be its capacity to prevent the formation of free radicals. Increasing the levels of antioxidant enzymes due to exercise in different parts of the brain can increase its antioxidant capacity. Recently, it has been suggested that exercise may prevent synaptic abnormalities in the hippocampus of diabetic rats and improve cognitive function in diabetic patients (34). Given the connection between oxidative stress, diabetes, and Aβ, regular physical activity helps modulate resistance to oxidative stress and increases antioxidant enzyme levels in the blood. Exercise is one of the most potent promoters of neurogenesis. Running on a rotating wheel increases the production and survival of new neurons (neurogenesis) in the dentate gyrus of the hippocampus by three to four times or even more (31). Based on this mechanism, it is likely that exercise training could reverse this pattern at the blood-brain barrier, facilitating the clearance of Aβ from the brain into the blood and reducing its accumulation in the brain (32). In a study by Cho et al. (2010), it was shown that exercise training may reduce brain Aβ plaque levels, possibly by regulating the processing of amyloid precursor protein or by enhancing the degradation and clearance of Aβ (35). Another potential mechanism for reducing brain Aβ following exercise training involves increased levels of LRP1 at the blood-brain barrier and a rise

in soluble plasma LRP1, which helps facilitate its clearance from the brain (31). While the exact mechanism regulating LRP1 at the blood-brain barrier remains unclear, exercise-induced increases in ADAM10 and ADAM17 promote the release of soluble plasma LRP1 (36). The potential connection between diabetes and Aβ lies in the fact that insulin deficiency is an early event that disrupts insulin signaling in the brain and is involved in the behavioral abnormalities associated with diabetes.

Furthermore, disturbances in insulin signaling are considered a precursor to the development of diabetes and may result from insulin deficiency (type 1 diabetes) or insulin resistance (type 2 diabetes). Reduced insulin signaling is linked to increased levels of Aβ protein. Specifically, Aβ protein levels in the brains of diabetic mice are significantly elevated (37). Therefore, the results of the present study align with findings from other studies that reported an increase in Aβ1-42 levels following the induction of diabetes (31, 36).

CONCLUSION

A review of previous research findings, along with the results of the current study, suggests that HIIT exercise training can influence the reduction of the pathological factors associated with diabetes and may play a role in controlling the progression of the disease in elderly individuals.

APPLICABLE REMARKS

- Based on the findings of the present study, the HIIT training strategy can be effective in (reducing) the pathological symptoms of diabetes and controlling the progression of this disease in the elderly.

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AUTHORS' CONTRIBUTIONS

Study concept and design: Marzieh Sadat Azarniveh. Acquisition of data: Asma Taheri. Analysis and interpretation of data: Mitra Khademosharie. Drafting the manuscript: Halimeh Vahdatpoor. Critical revision of the manuscript for important intellectual content: Frank Balaghi Inaloo. Statistical analysis: Marzieh Sadat Azarniveh. Administrative, technical, and material support: Marzieh Sadat Azarniveh. Study supervision: Mitra Khademosharie.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest in this article.

FINANCIAL DISCLOSURE

There are no financial interests related to the material in the manuscript.

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ETHICAL CONSIDERATION

The ethical committee of Shahid Sadoughi University of Medical Sciences, Yazd, Iran, approved this research. All animals received humane care according to the criteria outlined in the "Guide for the Care and Use of Laboratory Animals" prepared by the National Academy of Sciences and published by the National Institutes of Health (NIH publication 86-23 revised 1985).

ROLE OF THE SPONSOR

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ARTIFICIAL INTELLIGENCE (AI) USE

Artificial intelligence (AI) was not used in any capacity to develop, draft, or edit writing, nor was it used in data processing and analysis.

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