

## Research Article

# Impact of high-intensity interval training on ASC inflammasome, lipid profile and their correlation in diabetic rat model

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## Abstract

In Diabetes (Di) exercise training especially high-intensity interval training (HIIT) reduce blood lipids and improve anti-inflammatory status. In this study, we aimed to investigate the impact of high-intensity interval training on ASC inflammasome, lipid profile, and their correlation in diabetic rat models. Twenty rats were divided into four groups, including a control group, HIIT, Di, and Di+HIIT (n=5 in each group). Diabetes was induced using a combination of a high-fat diet (HFD) and STZ. Wistar rats in the exercise groups were subjected to high-intensity interval training for eight weeks. After sample collection, liver tissue was removed and weighed. Serum levels of lipid profile were measured by special kit. Protein expression of the apoptosis-associated speck-like protein containing a caspase activation and recruitment domain (ASC) in liver tissue was determined by Western blot. The results of the present study showed that diabetes induction significantly increased LDL, cholesterol, triglyceride and ASC levels and decreased HDL levels ( $p < 0.05$ ), whereas HIIT exercise training with diabetes somewhat adjusted the lipid profile and decreased the ASC inflammasome levels ( $p < 0.05$ ). In the correlation analysis, only the correlation between ASC and triglycerides was confirmed in the Di+HIIT group ( $p = 0.043$ ,  $r = 0.997$ ). Diabetes induction adversely affects lipid profiles and increases ASC inflammasome levels. However, high-intensity interval training (HIIT) appears to mitigate these effects by improving the lipid profile and reducing ASC levels. Notably, a significant positive correlation between ASC and triglycerides was observed in the diabetic rats undergoing HIIT, suggesting a link between inflammation and lipid metabolism.

**Key Words:** Inflammasome, ASC, Correlation, HIIT, Liver, Diabetes

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## Introduction

Diabetes mellitus is accompanied by hyperglycemia and dyslipidemia (Feingold & Grunfeld, 2023). The main reason for this disease is the inability of  $\beta$ -cells of the islets to produce insulin, which occurs either due to a wrong lifestyle or due to genetic reasons (Charles & Leslie, 2021). Due to the damage to various tissues of the body and the involvement of almost the entire body due to impaired glucose homeostasis, this disease imposes a huge burden on modern societies. The metabolic tissue of the liver is one of the important tissues involved in diabetes and bears high pressure due to the metabolic destruction of glucose and fat (Kim et al., 2021). The damage to the liver tissue of diabetes is so important that the term diabetic liver has also been spread due to the development of cirrhosis caused by diabetes (Qadri & Yki-Järvinen, 2024). Clinical observations confirm that the reduction in life expectancy in patients with diabetes is associated not only with cardiovascular complications, but also with cirrhosis and hepatocellular carcinoma (HCC) (Mallet et al., 2022).

The role of inflammation and inflammasomes in the pathophysiology and progression of diabetes mellitus (DM), which includes both type 1 (T1D) and type 2 (T2D), is crucial (Gora et al., 2021). As part of the innate immune system, NLRP3 is an inflammasome responsible for chronic inflammation induced by hyperglycemia. In both conditions, NLRP3 facilitates the release of interleukin-1 $\beta$  and interleukin-18 (Li et al., 2021). In T1D, NLRP3 perpetuates the autoimmune cascade and leads to the destruction of pancreatic islet cells. Another inflammasome is the apoptosis-associated speck-like protein containing a caspase activation and recruitment domain (ASC), which is also involved in diabetes. The liver ASC inflammasome plays a significant role in diabetes, particularly through its involvement in inflammation and metabolic regulation. The ASC (apoptosis-associated speck-like protein containing a CARD) is a critical component of the NLRP3 inflammasome, which is activated during states of chronic low-grade inflammation commonly seen in diabetes (Menini et al., 2020). Recent studies have further elucidated the role of infla-

-mmasomes in diabetic complications (Zhang et al., 2022) and the potential of exercise to modulate these inflammatory pathways (Liu et al., 2023). For instance, high-intensity interval training has been shown to impact systemic inflammation and improve metabolic outcomes in individuals with type 2 diabetes (Smith, 2024).

One of the important strategies to combat diabetes and control its complications is to modify lifestyle with regular exercise (Kanaley et al., 2022). Endurance exercise has been shown to reduce adipose tissue and body weight, insulin resistance, adipose tissue inflammation, and non-alcoholic fatty liver disease (NAFLD) (Keating et al., 2015). Recent studies have shown that high-intensity interval training (HIIT) reduces blood glucose in people with type 2 diabetes, independent of weight loss (Jelleyman et al., 2015; Mateo-Gallego et al., 2022). However, the affected organs and the mediating mechanisms are not known, especially in reducing inflammasomes. Intense exercise can be effective in reducing inflammation and controlling liver fat. However, its effects on ACS in diabetic liver tissue have not been carefully investigated. Therefore, the aim of the present study was to investigate the effect of high-intensity interval training on ASC inflammasome, lipid profile and their correlation in diabetic rat models.

## Materials and Methods

### Animals

Twenty male Wistar rats, weighing between 190 and 210 grams, were collected and brought to the animal laboratory at Ahvaz University in Khuzestan, Iran. The rats were housed in polycarbonate cages under standard conditions, including a humidity level of  $50 \pm 5\%$ , a temperature of  $22 \pm 2^\circ\text{C}$ , and a light/dark cycle of 12 hours each. They had unrestricted access to food and water. The ethical code for animal care (EE.1401.2.24.173155) from Ahvaz University approved all phases of the experiment. Rats were randomly divided into four groups, including a control group, HIIT, Di, and Di+HIIT (n=5 in each group). The control group remained sedentary throughout the study.

### Diabetes induction

To induce diabetes in the subjects, we administered a combination of a high-fat diet (HFD) for five weeks along with a single subcutaneous injection of streptozotocin (STZ), which was prepared in a 0.1 M citrate buffer at pH 4.5, with a dosage of 35 mg/kg sourced from Sigma-Aldrich, USA. Following a 72-hour period, we measured fasting blood glucose (FBG) levels using a glucometer (Acu-Chek Active, Roche, Germany) to confirm the presence of diabetes. Animals exhibiting FBG levels above 150 mg/dL were classified as diabetic.

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### Exercise training protocol

To familiarization the rats to the treadmill, they were allowed to run for 5 to 10 minutes at a speed of 5 to 10 m/min over the course of one week. The maximum speed test was employed to assess training intensity. Initially, the animals warmed up for 5 minutes at a speed of 5 m/min before starting the test at 9 m/min for 5 minutes. Following this, the treadmill speed was incrementally increased by 0.3 km/h every 3 minutes, in line with previous research. The point at which a rat could no longer continue running was recorded as its  $\text{VO}_{2\text{max}}$  speed (Leandro et al., 2007).

The HIIT program comprised four sessions each week, with each session lasting 45 minutes over a period of 8 weeks. It involved five intervals of 4 minutes at an intensity of 85-95%  $\text{VO}_{2\text{max}}$  followed by active rest periods of 3 minutes at 50-60%  $\text{VO}_{2\text{max}}$ . Each session of HIIT included a warm-up and a cool-down phase. The intensity (85-95%  $\text{VO}_{2\text{max}}$ ) was determined based on the maximum speed test conducted before the training program. To ensure the rats maintained the target intensity throughout the study, we monitored their running speed and adjusted the treadmill speed as needed based on observed fatigue levels.

### Laboratory measurements

To avoid any misinterpretation of data resulting from the residual effects of the last exercise session, rats were euthanized under deep anesthesia (administered intraperitoneally with Ketamine/Xylazine) 48 hours after the final exercise. Blood samples were collected from the animals' hearts. Each rat's liver was excised and dissected within four minutes, followed by rinsing with normal saline to remove any excess surface blood. Subsequently, the livers were placed in liquid nitrogen for two minutes and then stored at  $-80^\circ\text{C}$  for future analysis.

### Lipid profile

Serum LDL, HDL Cho, and triglyceride levels were measured using the Pars Azmoun kit in the university laboratory using an autoanalyzer.

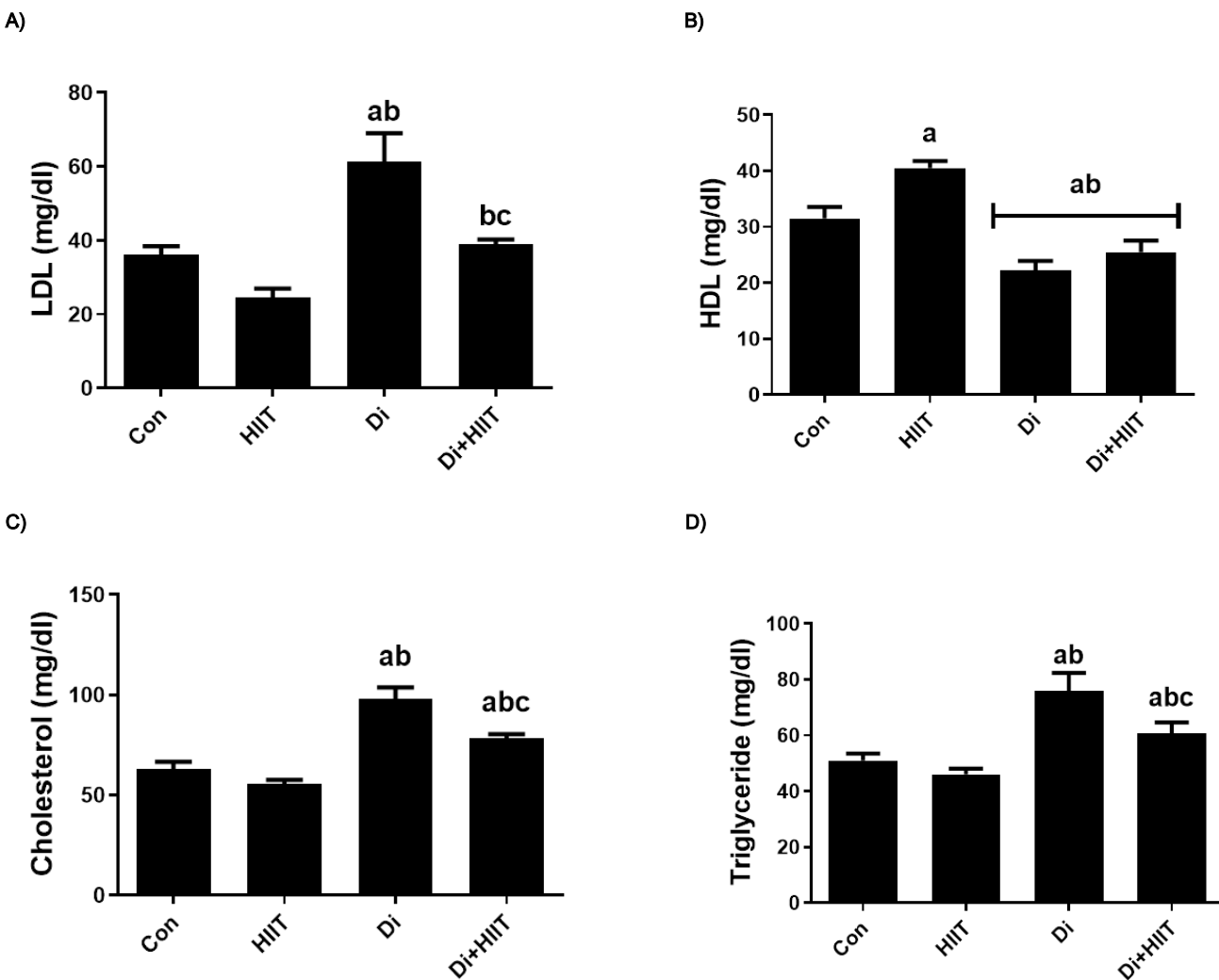
### Western blot

Western blotting was used to examine ASC protein. After lysis, the protein was separated by PAGE-SDS using a 12% Glycine-Tris gel (Invitrogen) and the protein was examined using a Western blotting machine manufactured by BioRad, England. Western blotting was performed using the primary antibody (Abcam) (1:1000 dilution). Then, it was reacted with the corresponding secondary HRP-conjugated antibodies (Abcam, USA, dilution: 1:2000). Finally, the blot was detected using the ECL diagnostic system (Amersham Life Science Inc., Arlington). The images obtained from the bands of the ASC protein were analyzed using ImageJ software. To ensure equal amounts of

protein at the time of measurement, the protein concentration was determined by the Lowry method before performing the assay. GAPDH protein was used as an internal control in this study.

### Statistical analyses

The data are presented as Mean  $\pm$  SD. To assess the normality of the data distribution and the homogeneity of variances, Shapiro-Wilk and Levene's tests were conducted. For analyzing differences between groups, one-way ANOVA with Tukey's post hoc test was utilized. Additionally, the relationship between variables across different groups was examined using the Pearson correlation test. The analyses and graphing were performed using SPSS Statistics software (Version 26) and GraphPad Prism 9. In this study, a p-value of less than 0.05 was deemed statistically significant.



**Figure 1.** Lipid profile (A: LDL, B: HDL, C: Cholesterol, D: Triglyceride) at different groups of study. Data were show as means  $\pm$  SD. a: sign of significant compare to Con group ( $p < 0.05$ ), b: sign of significant compare to HIIT group ( $p < 0.05$ ), c: sign of significant compare to Di group ( $p < 0.05$ ). Abbreviation: Con: Control, HIIT: High Intensity Interval Training, Di: Diabetes.

**Table 1.** Pierson correlation between ASC and lipid profile at different groups of study.

Variables	ASC			
	Con	HIIT	Di	Di+HIIT
<b>LDL</b>	r=-0.668 p=0.534	r=-0.237 p=0.847	r=-0.935 p=0.229	r=0.561 p=0.620
<b>HDL</b>	r=0.511 p=0.658	r=0.551 p=0.628	r=0.203 p=0.869	r=0.749 p=0.461
<b>Cholesterol</b>	r=0.656 p=0.544	r=0.487 p=0.675	r=-0.988 p=0.098	r=0.979 p=0.127
<b>Triglyceride</b>	r=-0.949 p=0.202	r=0.112 p=0.928	r=0.979 p=0.129	r=0.997 p=0.043*

Abbreviation: Con: Control, HIIT: High Intensity Interval Training, Di: Diabetes.\*: Sign of significant  $p < 0.05$

## Results

### Lipid profile

Lipid profile changes in different study groups are shown in Figure 1 (A-D). LDL values in the diabetic group showed a significant increase compared to the control and HIIT groups. In contrast, Di+HIIT showed a significant decrease in LDL compared to the Di group ( $p < 0.05$ ) (Fig 1A). HDL values, however, showed the opposite changes to LDL. As can be seen in Figure 1B, HDL in the HIIT group showed a significant increase compared to the healthy control group ( $p < 0.05$ ). In contrast, the Di and Di+HIIT groups showed a significant decrease in HDL compared to Con and HIIT. Changes in cholesterol and triglycerides were also similar (Fig 1C&D). Thus, diabetes caused a significant increase in cholesterol and triglycerides compared to the Con and HIIT groups ( $p < 0.05$ ). However, HIIT training treatment reduced cholesterol and triglycerides compared to the diabetic group, which were significant ( $p < 0.05$ ).

### ASC protein expression

In the present study, ASC protein expression levels were evaluated by Western blotting (Figure 2). As can be seen in Figure 2, ASC inflammasome levels were significantly increased in the diabetic groups. In other words, ASC protein showed a significant increase in the diabetic and Di+HIIT groups compared to the Con and HIIT groups ( $p < 0.05$ ). However, the Di+HIIT group showed a significant decrease in liver tissue ASC protein compared to the Di group ( $p < 0.05$ ).

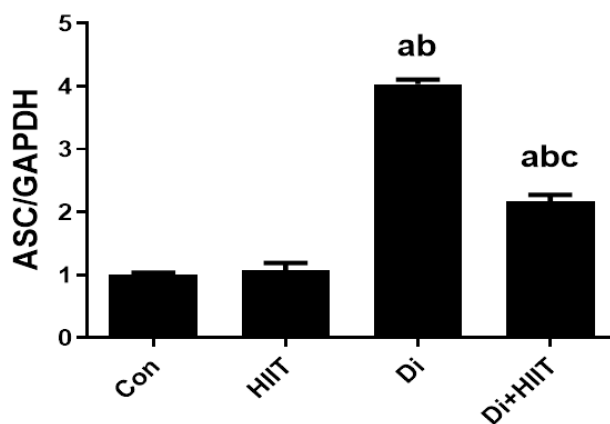
### Pierson correlation

In the present study, Pearson correlation test was used to examine the relationship between ASC inflammasome and individual lipid profile variables (Table 1). However, as can be seen in Table 1, the correlation between ASC variable and lipid profile including (HDL, LDL, Cholesterol, and Triglyceride) was not significant. Only the correlation between ASC and triglyceride was confirmed in the Di+HIIT group ( $p = 0.043$ ,  $r = 0.997$ ).

## Discussion

In diabetes, patients are usually at risk of extensive damage, including liver disorders, glycogen hepatopathy, nonalcoholic fatty liver disease, cirrhosis, and liver fibrosis (Mobasheri et al., 2023). The pathophysiological mechanisms of liver tissue damage caused by diabetes are complex. Among the liver damage caused by diabetes is the spread of inflammation and the destruction of its metabolism (Lindfors et al., 2025). In other words, diabetes leads to the accumulation of fatty acids, an increase in reactive oxygen species, an increase in advanced glycation end products, an increase in apoptosis and necrosis, and the promotion of fibrosis in the liver (Stefan & Cusi, 2022). Numerous studies have shown that exercise training, especially HIIT training, has antihyperglycemic and anti-inflammatory properties and also has beneficial effects on the complications of diabetes. Therefore, in the present study we investigate The impact of high-intensity interval training on ASC inflammasome, lipid profile and their correlation in diabetic rat models.

Based on the results of the present study, diabetes induction significantly increased LDL, cholesterol and triglyceride levels, which HIIT training was able to reduce in the serum levels of diabetic rats. However, diabetes reduced HDL, which training co-



**Figure 2.** Protein expression of ASC at different groups of study with Western Blot technique. Data were show as means  $\pm$  SD. a: sign of significant compare to Con group ( $p < 0.05$ ), b: sign of significant compare to HIIT group ( $p < 0.05$ ), c: sign of significant compare to Di group ( $p < 0.05$ ), Abbreviation: Con: Control, HIIT: High Intensity Interval

uld not increase. Based on the results of the present study, diabetes is associated with a set of metabolic disorders. The American Diabetes Association (ADA) defined non-dyslipidemic lipid levels for adults with type 2 diabetes as low-density lipoprotein (LDL) <100 mg/dL, high-density lipoprotein cholesterol (HDL-C) >40 g/dL in men and >50 mg/dL in women, triglycerides (TG) <150 mg/dL, and total cholesterol <200 mg/dL (Solano & Goldberg, 2006). Although the present study used an animal model, it can be stated that diabetes leads to the destruction of homeostasis in the lipid profile. According to studies, the prevalence of diabetic dyslipidemia in patients with type 2 diabetes is 72 to 85% and is associated with an increased risk of cardiovascular diseases (Athyros et al., 2018). The components of diabetic dyslipidemia include increased levels of total cholesterol (TC), TG, LDL, and decreased levels of HDL (Solano & Goldberg, 2006). According to these interpretations, the prevalence of dyslipidemia caused by diabetes can also be estimated in the present study. However, more measurements are needed to confirm this hypothesis. In contrast, it seems that interval training can control this increase in lipid factors caused by diabetes. Consistent with the results of the present study, Feng et al. (2024) showed that performing HIIT exercises can improve lipid and blood sugar profiles in people with type 2 diabetes (Feng et al., 2024). The effectiveness of interval training in reducing body fat and weight has been proven. It seems that high-intensity interval training can also play a role in regulating blood lipids by increasing fat metabolism and increasing FFA consumption.

In addition, the observed changes in LDL, HDL, cholesterol, and triglycerides are consistent with the dyslipidemia commonly observed in type 2 diabetes in humans. Specifically, the increase in LDL, cholesterol, and triglycerides, and the decrease in HDL, are all hallmarks of diabetic dyslipidemia. These changes are associated with an increased risk of cardiovascular disease. The fact that HIIT was able to partially reverse these changes suggests that it may be a useful therapeutic intervention for improving lipid profiles in diabetic patients.

In addition to the lipid profile, in the present study, the levels of ASC inflammasomes were significantly increased in the diabetic groups. However, the Di+HIIT group showed a significant decrease in liver tissue ASC protein compared to the Di group. In examining the relationship between lipid profile and ASC, only the correlation between ASC and triglycerides was confirmed in the Di+HIIT group. The increase in inflammasomes in diabetes has been almost proven. It has been stated that Nlrp3 inflammasome activated in type 2 diabetes (Dixit, 2012). Diabetes significantly affects the activation of inflammasomes, including NLRP3, particularly in the liver, which has implications for insulin resistance and liver injury. Inflammasomes are a critical component of the innate immune system that responds to various

metabolic stressors, including those associated with diabetes. The relationship between diabetes and the ASC protein is primarily through the NLRP3 inflammasome, which plays a critical role in insulin resistance and inflammation associated with type 2 diabetes (Lu et al., 2023). In other words, the effect of ASC appears to be mediated through NLRP3. Because ASC is a critical component of the NLRP3 inflammasome, which is activated in response to various metabolic stressors, such as obesity and high-fat diets. In type 2 diabetes, there is an increased accumulation of danger-associated molecular patterns (DAMPs) that cause the accumulation of NLRP3 inflammasome, which leads to the activation of caspase-1 and the subsequent secretion of proinflammatory cytokines such as IL-1 $\beta$  and IL-18. These cytokines contribute to insulin resistance and organ dysfunction (Grant & Dixit, 2013). In the present study, although NLRP3 and inflammatory cytokines were not evaluated, it seems that the increase in ASC through the aforementioned pathways plays a role in the development of diabetic damage, and HIIT exercise training can have a protective role by regulating it, especially in liver tissue. Liang et al (2020) show that high-intensity interval training and moderate-intensity continuous training alleviate  $\beta$ -amyloid deposition by inhibiting NLRP3 inflammasome activation in APPswe/PS1dE9 mice (Liang et al., 2020). Therefore, this type of exercise can reduce inflammasome at diabetic animal. The confirmed correlation between ASC and triglycerides in the Diabetes+HIIT group highlights the complex interplay between lipid metabolism and inflammation in diabetes management. The findings suggest that elevated triglycerides may serve as a trigger for ASC-mediated inflammation, which could worsen insulin resistance. Further studies are needed to elucidate the precise mechanisms linking triglycerides and ASC activation in various populations. Investigating how different types of exercise affects this relationship could provide insights into optimizing diabetes management strategies.

The significant correlation between ASC and triglycerides in the Di+HIIT group suggests that HIIT may modulate the relationship between inflammation and lipid metabolism in diabetic rats. While there is limited direct evidence from other studies to support this specific finding, there is evidence that exercise can reduce both inflammation and triglyceride levels in diabetic patients [Reference to relevant studies]. The lack of significant correlations in the other groups may indicate that the relationship between ASC and lipid profile is complex and context-dependent, and that HIIT may be necessary to unmask this relationship.

A limitation of this study is the small sample size (n=5 per group), which limits the generalizability of the findings. Future studies with larger sample sizes are needed to confirm these results. Another limitation is the absence of additional markers of inflammation (e.g., NLRP3, IL-1 $\beta$ , IL-18), which would have provided a more comprehensive understanding of the inflammas-

-ome pathway. Future studies should include these markers.

### Clinical implications

Despite these limitations, our findings have potential clinical implications for the use of HIIT as a therapeutic intervention for diabetic patients. HIIT has been shown to improve glycemic control, reduce cardiovascular risk factors, and enhance overall fitness in individuals with type 2 diabetes. Our results suggest that HIIT may also have beneficial effects on inflammation and lipid metabolism in diabetic patients. Further research is needed to determine the optimal HIIT protocols for diabetic patients and to evaluate the long-term effects of HIIT on diabetes-related complications

### Conclusion

In summary, the findings of this study indicate that diabetes induction leads to a detrimental alteration in the lipid profile, characterized by elevated levels of LDL, cholesterol, triglycerides, and ASC, alongside a reduction in HDL levels. However, the implementation of high-intensity interval training (HIIT) in diabetic subjects appears to positively influence these lipid parameters and reduce ASC inflammasome levels. Notably, a significant correlation was observed between ASC and triglycerides in the Di+HIIT group, suggesting a potential link between inflammasome activity and lipid metabolism in the context of diabetes. These results underscore the beneficial effects of HIIT as an intervention for improving lipid profiles and modulating inflammatory responses in diabetic conditions.

### What is already known on this subject?

The role of inflammation and inflammasomes in the pathophysiology and progression of diabetes mellitus (DM), which includes both type 1 (T1D) and type 2 (T2D), is crucial.

### What this study adds?

the implementation of HIIT in diabetic subjects appears to positively influence these lipid parameters and reduce ASC inflammasome levels.

#### Organ Cross-Talk Tips:

- High-intensity interval training (HIIT) may enhance communication between metabolic and inflammatory pathways, thereby promoting better metabolic health.

### Acknowledgements

None.

### Funding

No sources of funding were sought or awarded for this study.

### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** The ethical code for animal care (EE.1401.2.24.173155) from Ahvaz University approved all phases of the experiment.

**Informed consent** Animal study.

### Author contributions

Conceptualization: R.Sh., S.Sh., M.R.T.; Methodology: R.Sh., S.Sh., M.R.T.; Software: R.Sh.; Validation: S.Sh., Formal analysis; Investigation: M.R.T.; Resources: R.Sh., S.Sh., M.R.T.; Data curation: M.R.T.; Writing - original draft: R.Sh.; Writing - review & editing: R.Sh., S.Sh., M.R.T.; Visualization: R.Sh., S.Sh., M.R.T.; Supervision: S.Sh. Project administration: R.Sh.; Funding acquisition: S.Sh.

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