



The Effect of Eight Weeks of High-Intensity Interval Training with L-Cysteine Consumption on CRP and TNF- α in Heart Tissue of Young Rats with Type 2 Diabetes

Mana Davoudi¹, Akbar Nouri Habashi^{1*}, Behrouz Baghaiee²

¹Department of Exercise Physiology, Faculty of Sport Science, Urmia University, Urmia, Iran

²Department of Physical Education and Sport Science, Aras Branch, Islamic Azad University, Jolfa, Iran

Abstract

Background: This study aimed to investigate the effect of 8-weeks of high-intensity interval training (HIIT) with L-cysteine consumption on tumor necrosis factor-alpha (TNF- α) and C-reactive protein (CRP) of heart tissue in young rats with type 2 diabetes.

Methods: The statistical population of the present study consisted of young (4 months) rats with type 2 diabetes. Ten rats were selected as a healthy group, and 40 rats became diabetic. Diabetic rats were randomly divided into four groups: diabetes control, diabetics with training, diabetics with supplements, and diabetics with training+supplement. Moreover, high-intensity interval exercises were performed 3 days a week for 8 weeks, and 500 micromoles of L-cysteine were administered daily.

Results: The training+supplement group had significantly higher TNF- α levels compared to the diabetic control group ($P=0.002$). The diabetic control group ($P=0.001$) and training group ($P=0.001$) had higher TNF- α levels compared to the healthy control. The supplement group had significantly less TNF- α compared to the diabetic control group ($P=0.003$), while the supplement group ($P=0.019$) and the training+supplement group ($P=0.013$) had lower TNF- α levels compared to the training group. Moreover, the training+supplement group had lower CRP levels compared to the diabetic control group ($P=0.001$), while the diabetic control ($P=0.001$), exercise ($P=0.002$), and supplement group ($P=0.031$) had higher CRP levels compared to the healthy control. Moreover, the training group ($P=0.038$) and the supplement group ($P=0.002$) had lower CRP compared to the diabetic control group. Furthermore, the training+supplement group had a lower CRP level compared to the training group ($P=0.03$).

Conclusion: HIIT along with the L-cysteine consumption reduced TNF- α and CRP in the heart tissue of diabetic rats.

Keywords: Type 2 diabetes, Inflammation, High-intensity interval training, L-cysteine

*Correspondence to

Akbar Nouri Habashi,
Email: Abarnori52@gmail.
com



Received: May 6, 2023, Accepted: June 4, 2023, ePublished: September 30, 2023

Introduction

As the vascular complications of diabetes are partly caused by inflammatory processes, reducing inflammation may not only improve blood sugar control and reduce impaired beta-cell secretion but also prevent diabetes. Some studies have demonstrated that tumor necrosis factor-alpha (TNF- α) is one of the important pro-inflammatory mediators in insulin resistance and β -cell damage (1). The pro-inflammatory cytokine TNF- α is an important molecule in the development of insulin resistance. These results were obtained in cultured cells and TNF- α knockout rats (2). Furthermore, in healthy individuals, TNF- α inhibits peripheral insulin-stimulated glucose uptake by disrupting the phosphorylation of the substrate Akt 160, which is a key step in the

canonical regulation of insulin signaling and the glucose transporter type 4 cascade and canonical insulin signaling transduction. It prevents the absorption of glucose and signal transmission by insulin in the whole body (2). In addition, a small increase in C-reactive protein (CRP) predicts the possibility of cardiovascular disease in non-diabetic and diabetic people (1). It is expressed in human vascular cells, and atherosclerotic plaques and monocytes/macrophages are important sources of CRP (3). CRP is produced via the activity of the main cells in atherosclerotic lesions, which may contribute to the development or progression of atherosclerosis in coronary plaques. Several studies have indicated that some inflammatory factors associated with diabetes such as free fatty acids and modified lipoproteins, adipokines,

and high glucose may cause CRP production (3). These results suggested that the CRP level in atherosclerotic plaques of diabetic samples can be higher than that in non-diabetic plaques. Given the possible association between local CRP levels and the severity of coronary artery disease, these changes may contribute to the progression of vascular disease in patients with type 2 diabetes (3). The stimulation of CRP synthesis has also been reported to occur mainly in response to pro-inflammatory cytokines, particularly interleukin 6 (IL-6), TNF- α , and interleukin-1 (IL-1) (4).

Using appropriate food supplements and exercising can be effective in reducing the complications of diabetes. L-cysteine can be mentioned among these supplements. Cysteine is an amino acid with the formula $(SCH_2CH(NH_2)CO_2H)_2$, which is produced in the human body from the oxidation of two cysteine molecules that form a disulfide bond together. L-cysteine has anti-inflammatory effects (5). Various studies have shown that L-cysteine supplementation leads to the improvement of blood sugar or vascular inflammation in diabetic animals or normal models. In this regard, after 8 weeks of L-cysteine supplementation, rats that received the supplement had significantly lower levels of glycated hemoglobin and glucose compared to rats that did not receive L-cysteine (6). According to studies, diabetic subjects had lower blood levels of H₂S and L-cysteine, as well as altered cysteine homeostasis (7). In addition, the results have indicated that feeding with L-cysteine and Na₂S reduces the phosphorylation of NF- κ B and the secretion of TNF- α , monocyte chemoattractant protein-1, interleukin-8, IL-1 β , and interferon gamma-induced protein 10. Treatment with L-cysteine (500 μ M), Na₂S (25 μ M), and PIP3 (5 nM) increased the phosphorylation of AMP-activated protein kinase and peroxisome proliferator-activated receptor gamma expression in cells exposed to high glucose (8). However, no specific results have been reported regarding the effects of L-cysteine consumption on TNF- α and interleukin-13 in diabetic samples.

On the other hand, a large number of cross-sectional, prospective, and retrospective studies have reported a significant relationship between exercise training and type 2 diabetes (9). Considering the role of TNF- α in increasing insulin resistance, training may increase insulin sensitivity by suppressing TNF- α (3). Interval training programs have attracted increasing attention in recent years. A landmark study was conducted by Tjønnå et al who compared continuous exercise with aerobic high-intensity interval training (HIIT) over 12 weeks in individuals with metabolic syndrome. Their results showed that interval training improves factors affecting metabolic syndrome despite the fact that the training volume differed between the two groups (10). Following this, other studies investigated the effect of interval

training on people with metabolic disease, especially people with type 2 diabetes (11,12). In general, HIIT is superior in improving metabolic indices compared to continuous training. Despite the favorable effects of periodic exercise on diabetic patients, it leads to better effects if it is combined with a supplement such as L-cysteine. Therefore, this research aimed to investigate the effect of 8 weeks of high-intensity intermittent exercise along with L-cysteine consumption on the level of CRP and TNF- α in the heart tissue of young rats with type 2 diabetes.

Materials and Methods

The present research is experimental. The statistical population of the present study was composed of young (4 months) diabetic mice. To this end, 50 rats were purchased from one of the research centers and then placed in laboratory conditions with free access to water and food, as well as 12 hours of light and 12 hours of darkness. Then, some diabetic rats developed diabetes. Streptozotocin was used as a single dose in diabetic rats, and the induction of diabetes was done intravenously with a dose of 50 mg/kg streptozotocin, and blood sugar above 250 mg/kg one week after injection was considered induced diabetes. Then, the rats were divided into five groups: healthy control (HC), diabetic control (DC), diabetic with training (DT), diabetic with supplementation (DS), and diabetic with training and supplementation (DTS). HIIT was performed 3 days a week. Supplements were also injected into rats, and 48 hours after all training and supplementation, the rats were anesthetized, and their heart was removed.

Planning of the Correction and Frequency

HC (10 rats): The rats had their normal life.

DC (10 rats): This group was made diabetic intravenously with a dose of 50 mg/kg of streptozotocin.

DT (10 rats): This group became diabetic with a dose of 50 mg/kg streptozotocin intravenously and then performed interval training for 8 weeks.

DS (10 rats): This group was treated with a dose of 50 mg/kg of streptozotocin. Then, 1/5 tablet of L-cysteine (200 mg; Hexal; Germany 3) was dissolved in 3 mL water and was administered daily by gavage (500 μ mol).

DTS (10 rats): This group was made diabetic with a dose of 50 mg/kg of streptozotocin intravenously, and then they participated in HIIT for 8 weeks. Afterward, 1/5 tablet of L-cysteine (200 mg; Hexal; Germany 3) was dissolved in 3 mL water and was administered daily by gavage (500 μ mol).

Interval Training Protocol

The HIIT protocol included 10 bouts of 2 minutes running on a rodent treadmill (Technic Azma, Iran) at 90% VO₂max with 60 seconds of rest at a speed of

20 meter/minute in the first week, and the speed was gradually increased to 30 m/min in 8 weeks (no slope). Moreover, the warming and cooling down time was 5 minutes (13), as observed in Table 1.

L-Cysteine Consumption Protocol

First, 1.5 L-cysteine tablets (200 mg; Hexal; Germany) were dissolved in 3 mL of water and administered daily by soluble gavage (500 μ mol). The dose of L-cystine was proportional to the dose of the human being and was calculated based on the human-to-animal formula (14). Sampling was performed 48 hours after the last training session and after a fasting night. To collect samples, the rats were first anesthetized using a combination of xylazine (10 mg/kg) and ketamine (100 mg/kg) via intraperitoneal injection. Then, the hearts of the rats were extracted and, after washing in physiological serum, were immediately frozen in liquid nitrogen and maintained in a freezer at -80.

Enzyme-Linked Immunosorbent Assay Testing Method

Levels of TNF- α and CRP were assayed in the heart tissue lysate sample by the enzyme-linked immunosorbent assay kits (TNF- α : DuoSet Development Kit Catalog Numbers DY510-05, CRP: DuoSet Development Kit Catalog Number: DY1744).

Statistical Method

In this study, the Kolmogorov-Smirnov test was used to evaluate the normal data distribution. The one-way analysis of variance (ANOVA) test was also used to compare the inter-group, and the Tukey post hoc test was employed to compare the two groups. All reviews were performed using SPSS 22 (Chicago) software at a significant level of $P \leq 0.05$.

Results

Table 2 illustrates the body weight. As observed, body weight in the DC group increased significantly compared to the HC ($P=0.02$). However, there was a significant decrease in the DTS group compared to the DC group ($P=0.04$), but there was no significant change in body

weight in the DT group ($P=0.053$) and the DS group ($P=0.051$) compared to the DC group.

Moreover, there is a significant difference in terms of heart tissue TNF- α between the groups ($P=0.001$). The results of the Post hoc test showed that the DTS has significantly higher TNF- α levels compared to the DC group ($P=0.002$). Moreover, the DC group ($P=0.001$) and DT group ($P=0.001$) had higher TNF- α levels compared to the HC group. In addition, the DS group had significantly less TNF- α compared to the DC group ($P=0.003$), and the DS group ($P=0.019$) and the DTS group ($P=0.013$) had lower TNF- α levels compared to the DT group. However, there was no significant difference among other groups (Table 2 and Figure 1).

Furthermore, the results of the ANOVA statistical test showed that there is a significant difference between the groups in terms of CRP levels in the heart tissue ($P=0.001$). The results of the post hoc test also suggested that there is a significant difference between the DTS group compared to the DC group, and this group has a lower CRP value compared to the DC group ($P=0.001$). In addition, DC ($P=0.001$), DT ($P=0.002$), and DS ($P=0.031$) groups had higher CRP levels compared to the HC group. The DT group ($P=0.038$) and the DS group ($P=0.002$) had lower CRP compared to the DC group, and the DTS group had lower CRP levels compared to the DT group ($P=0.03$), as depicted in Table 2 and Figure 2.

Discussion

The results of this study indicated that the amount of TNF- α significantly increased in the DC group compared to the HC. Alzamil also reported that diabetes increases TNF- α (15). Additionally, the results showed that the amount of TNF- α in the DS group and the DTS group had a significant decrease compared to the diabetic control group. However, in terms of TNF- α , the DT group was not significantly different from the DC group. In addition, there was no difference between the DS group, the DTS group, and the HC group. Based on this finding, interval training alone did not have a significant effect on TNF- α in the heart tissue of diabetic rats, but it can reduce TNF- α along with L-cysteine consumption. On the other hand, the absence of a significant difference between the L-cysteine group and the training group with

Table 1. HIIT Training Protocol

Week	Slope	Speed	Time
1	0	20	10
2	0	20	10
3	0	22	10
4	0	22	10
5	0	24	10
6	0	26	10
7	0	28	10
8	0	30	10

Note. HIIT: High-intensity interval training.

Table 2. Weight in All Groups

Groups	Mean \pm SD (g)
HC	215 \pm 15
DC	273 \pm 12
DT	251 \pm 8
DS	244 \pm 8
DTS	233 \pm 8

Note. HC: Health control; DC: Diabetic control; DT: Diabetic + training; DS: Diabetic + supplement; DTS: Diabetic + training + supplement; SD: Standard deviation.

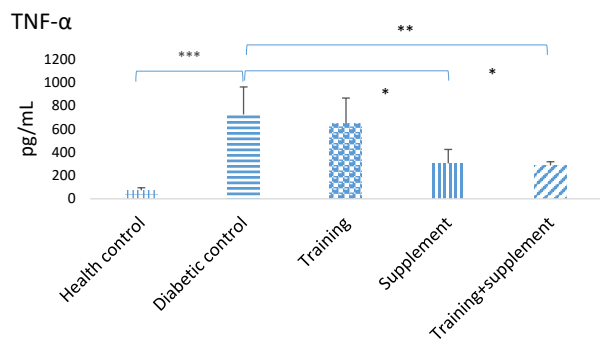


Figure 1. TNF- α Difference Between Groups. Note. TNF- α : Tumor necrosis factor-alpha; *: *P* value is less than 0.05; **: *P* value is less than 0.01; ***: *P* value is less than 0.001

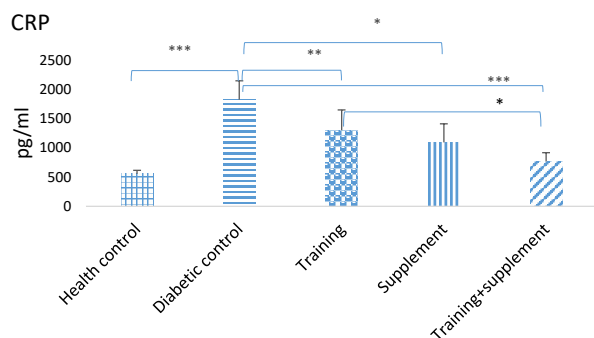


Figure 2. CRP Difference between Groups. Note. CRP: C-reactive protein; * *P* value is less than 0.05; ** *P* value is less than 0.01; *** *P* value is less than 0.001

L-cysteine and the HC group means that the consumption of L-cysteine alone and in interaction with exercise could make the amount of TNF- α very close to the values of healthy samples. Hence, it is an extremely important opinion.

Cell culture studies by Mana et al using a 3T3L1 fat cell model demonstrated that L-cysteine increases glucose metabolism and cellular phosphatidylinositol-3,4,5-triphosphate (PIP3) (16). In addition, the effect of L-cysteine supplementation on increasing glucose utilization and PIP3 levels was reduced by propargylglycine, a cystathionine γ -lyase inhibitor that catalyzes H2S formation. Furthermore, supplementation with L-cysteine, PIP3, or H2S increased insulin receptor substrate-1, PKC ζ /I phosphorylation, AKT, glucose transporter type 4 activation, and glucose utilization in cells treated with high glucose. L-cysteine has a potential anti-oxidative effect as an oxidant and glutathione precursor (17) and can also reverse the physiological effect of nitric oxide (NO) as a carrier of NO. It has been reported that L-cysteine may significantly inhibit NF- κ B activation and TNF- α release. This effect can be explained in the sense that L-cysteine can increase glutathione synthesis. This process prevents or regulates the imbalance of the redox reaction and the activation of the active enzyme I- κ B by reactive oxygen species and its derivatives

produced by the cell. As a result, it inhibits IL-1 β , TNF- α , and other inflammatory cytokines that are regulated by the NF- κ B signaling pathway (15). Furthermore, in terms of the effect of interval exercise alone, our findings are in contradiction with the findings of Samaie et al (18), Fasihi Ramandi and Khaledi (19), and Naghizadeh and Heydari (20). The intensity and duration of exercise may be the reason for the difference in results, but in general, interval exercise in interaction with L-cysteine decreased TNF- α . Exercise training was found to be effective in reducing TNF- α , its soluble receptors, and adhesive molecules in sick people, including people with impaired glucose tolerance. Research has shown that TNF- α can be reduced by exercise (19,20). The mechanism of TNF- α changes after interval training is stronger than its changes after moderate-intensity aerobic training. Factors such as the characteristics of the training program (e.g., the intensity and duration of the activity), the type of training program, and the duration of the training program can be effective in TNF- α changes (21). It also seems that increasing interleukin-13 is effective in reducing TNF- α (22).

The results of the present study indicated that the amount of CRP increased due to the induction of type 2 diabetes in the DC group compared to the HC, so they are consistent with the findings of Mazidi et al (23) and Atalar et al (24). The results also showed that the exercise group and L-cysteine consumption had lower CRP levels than the DC group. The exercise and L-cysteine groups also had lower CRP compared to the DC group, but more importantly, the training group with L-cysteine had a lower CRP value than the training group. In this regard, Mana et al also found that L-cysteine supplementation reduces blood glucose, glycosylated hemoglobin, and CRP and inhibits NF- κ B activation in the liver of diabetic rats (8). Naghizadeh and Heydari also investigated the effect of 12 weeks of HIIT on the IL-6, CRP, and TNF- α serum levels in men with hyperlipidemia and type 2 diabetes, reporting the reduction of IL-6, TNF- α , and CRP (20).

There are several potential mechanisms by which long-term exercise alters inflammatory regulation. The first mechanism is that exercise reduces gene expression and serum levels of leukocyte adhesion molecules, thus inhibiting the monocyte reaction of the endothelial cell. Another mechanism is that exercise training leads to the improvement of endothelial function by reducing factors that disrupt endothelial function. Moreover, exercise can improve endothelial function by increasing the release of NO; therefore, by improving endothelial function, inflammation is reduced, and in general, exercise helps prevent endothelial damage and inflammation (25). Another mechanism is that exercise leads to a decrease in the gene expression of cytokines by increasing protein synthesis and the production and release of myokines or by decreasing the daily hypoxia episodes that stimulate the

gene expression of pro-inflammatory cytokines through the production of free radicals. Moreover, it reduces the production of pro-inflammatory cytokines from mononuclear cells by strengthening the cardiovascular system (25).

On the other hand, other studies have revealed that oxidative stress may increase inflammation and neutralize antioxidants in hemodialysis patients. As a supplement with antioxidant effects, the effect of L-cysteine on the level of oxidative stress was evaluated (26). Shahbazian et al reported that the administration of L-cysteine reduces oxidative stress in hemodialysis patients (27). Giannikouris explained that L-cysteine significantly reduced inflammatory markers such as high-sensitivity CRP in dialysis patients (28).

Conclusion

The results of this study showed that type 2 diabetes increases CRP and TNF- α in the heart tissue of rats. However, intermittent exercise with L-cysteine decreased CRP and TNF- α .

Acknowledgements

This article is taken from an M.A. thesis in the field of Exercise Physiology at Urmia University.

Authors' Contribution

Conceptualization: Mana Davoudi.

Data curation: Mana Davoudi, Akbar Nouri Habashi, Behrouz Baghaiee.

Methodology: Mana Davoudi.

Project administration: Akbar Nouri Habashi.

Supervision: Akbar Nouri Habashi, Behrouz Baghaiee.

Writing—original draft: Mana Davoudi.

Writing—review & editing: Akbar Nouri Habashi, Behrouz Baghaiee.

Competing Interests

The authors have no conflict of interests.

Ethical Approval

This article was approved by the Ethics Committee of Urmia University with the code IR.URMIA. RES.1401.013.

Funding/Support

This article was financially supported by Urmia University.

References

- Pedersen BK. Anti-inflammatory effects of exercise: role in diabetes and cardiovascular disease. *Eur J Clin Invest.* 2017;47(8):600-11. doi: [10.1111/eci.12781](https://doi.org/10.1111/eci.12781).
- Karstoft K, Pedersen BK. Exercise and type 2 diabetes: focus on metabolism and inflammation. *Immunol Cell Biol.* 2016;94(2):146-50. doi: [10.1038/icb.2015.101](https://doi.org/10.1038/icb.2015.101).
- Mugabo Y, Li L, Renier G. The connection between C-reactive protein (CRP) and diabetic vasculopathy. Focus on preclinical findings. *Curr Diabetes Rev.* 2010;6(1):27-34. doi: [10.2174/157339910790442628](https://doi.org/10.2174/157339910790442628).
- Sproston NR, Ashworth JJ. Role of C-reactive protein at sites of inflammation and infection. *Front Immunol.* 2018;9:754. doi: [10.3389/fimmu.2018.00754](https://doi.org/10.3389/fimmu.2018.00754).
- Jariyamana N, Chuveera P, Dewi A, Leelapornpisid W, Ittichaicharoen J, Chattipakorn S, et al. Effects of N-acetyl cysteine on mitochondrial ROS, mitochondrial dynamics, and inflammation on lipopolysaccharide-treated human apical papilla cells. *Clin Oral Investig.* 2021;25(6):3919-28. doi: [10.1007/s00784-020-03721-7](https://doi.org/10.1007/s00784-020-03721-7).
- Jain SK, Velusamy T, Croad JL, Rains JL, Bull R. L-cysteine supplementation lowers blood glucose, glycated hemoglobin, CRP, MCP-1, and oxidative stress and inhibits NF-kappaB activation in the livers of Zucker diabetic rats. *Free Radic Biol Med.* 2009;46(12):1633-8. doi: [10.1016/j.freeradbiomed.2009.03.014](https://doi.org/10.1016/j.freeradbiomed.2009.03.014).
- Whiteman M, Gooding KM, Whatmore JL, Ball CI, Mawson D, Skinner K, et al. Adiposity is a major determinant of plasma levels of the novel vasodilator hydrogen sulphide. *Diabetologia.* 2010;53(8):1722-6. doi: [10.1007/s00125-010-1761-5](https://doi.org/10.1007/s00125-010-1761-5).
- Manna P, Jain SK. L-cysteine and hydrogen sulfide increase PIP3 and AMPK/PPAR γ expression and decrease ROS and vascular inflammation markers in high glucose treated human U937 monocytes. *J Cell Biochem.* 2013;114(10):2334-45. doi: [10.1002/jcb.24578](https://doi.org/10.1002/jcb.24578).
- Weinstein MC, Toy EL, Sandberg EA, Neumann PJ, Evans JS, Kuntz KM, et al. Modeling for health care and other policy decisions: uses, roles, and validity. *Value Health.* 2001;4(5):348-61. doi: [10.1046/j.1524-4733.2001.45061.x](https://doi.org/10.1046/j.1524-4733.2001.45061.x).
- Tjønnå AE, Lee SJ, Rognmo Ø, Stølen TO, Bye A, Haram PM, et al. Aerobic interval training versus continuous moderate exercise as a treatment for the metabolic syndrome: a pilot study. *Circulation.* 2008;118(4):346-54. doi: [10.1161/circulationaha.108.772822](https://doi.org/10.1161/circulationaha.108.772822).
- Mitranun W, Deerochanawong C, Tanaka H, Suksom D. Continuous vs interval training on glycemic control and macro- and microvascular reactivity in type 2 diabetic patients. *Scand J Med Sci Sports.* 2014;24(2):e69-76. doi: [10.1111/sms.12112](https://doi.org/10.1111/sms.12112).
- Robinson E, Durrer C, Simtchouk S, Jung ME, Bourne JE, Voth E, et al. Short-term high-intensity interval and moderate-intensity continuous training reduce leukocyte TLR4 in inactive adults at elevated risk of type 2 diabetes. *J Appl Physiol (1985).* 2015;119(5):508-16. doi: [10.1152/japplphysiol.00334.2015](https://doi.org/10.1152/japplphysiol.00334.2015).
- Yazdani F, Shahidi F, Karimi P. The effect of 8 weeks of high-intensity interval training and moderate-intensity continuous training on cardiac angiogenesis factor in diabetic male rats. *J Physiol Biochem.* 2020;76(2):291-9. doi: [10.1007/s13105-020-00733-5](https://doi.org/10.1007/s13105-020-00733-5).
- Amini Y, Moloudi R, Izadpanah E, Hassanzadeh K. N-acetylcysteine provides analgesic effect in rats. *J Isfahan Med Sch.* 2013;31(257):1682-9. [Persian].
- Alzamil H. Elevated serum TNF- α is related to obesity in type 2 diabetes mellitus and is associated with glycemic control and insulin resistance. *J Obes.* 2020;2020:5076858. doi: [10.1155/2020/5076858](https://doi.org/10.1155/2020/5076858).
- Manna P, Jain SK. Hydrogen sulfide and L-cysteine increase PIP3 and glucose utilization by inhibiting PTEN and activating PI3K/AKT/PKC in 3T3L1 adipocytes. *Free Radic Biol Med.* 2011(51):S63. doi: [10.1016/j.freeradbiomed.2011.10.163](https://doi.org/10.1016/j.freeradbiomed.2011.10.163).
- Zhang Q, Ju Y, Ma Y, Wang T. N-acetylcysteine improves oxidative stress and inflammatory response in patients with community acquired pneumonia: a randomized controlled trial. *Medicine (Baltimore).* 2018;97(45):e13087. doi: [10.1097/md.00000000000013087](https://doi.org/10.1097/md.00000000000013087).
- Samaie SS, Peeri M, Delfan M. The effect of high intensity interval training and continuous endurance training on gene expression of adiponectin and TNF- α in type 2 diabetic rats. *J Sport Biosci.* 2018;10(3):317-32. doi: [10.22059/](https://doi.org/10.22059/)

- jsb.2018.247817.1227. [Persian].
19. Fasihi Ramandi E, Khaledi N. High intensity interval training induced changes in the hepatic FGF-21 gene expression and serum TNF- α in diabetic male rats. *Research in Sport Medicine and Technology*. 2020;18(19):57-68. doi: [10.29252/jsmt.18.19.57](https://doi.org/10.29252/jsmt.18.19.57).
 20. Naghizadeh H, Heydari F. The effect of 12 weeks of high-intensity interval training and curcumin consumption on plasma levels of IL-6, TNF- α and CRP in men with type II diabetes along with hyperlipidemia. *Journal of Practical Studies of Biosciences in Sport*. 2023;11(25):22-36. doi: [10.22077/jpsbs.2022.4895.1682](https://doi.org/10.22077/jpsbs.2022.4895.1682). [Persian].
 21. Rezaei S, Khaledi N. The effect of high intensity interval training on serum TNF- α levels and FOXO1 gene expression of hippocampus in male diabetic Wistar rats. *J Sabzevar Univ Med Sci*. 2021;28(5):688-99. [Persian].
 22. Kazemi S, Vaisi-Raygani A, Keramat F, Saidijam M, Soltanian AR, Alahgholi-Hajibehzad M, et al. Evaluation of the relationship between IL-12, IL-13 and TNF- α gene polymorphisms with the susceptibility to brucellosis: a case control study. *BMC Infect Dis*. 2019;19(1):1036. doi: [10.1186/s12879-019-4678-8](https://doi.org/10.1186/s12879-019-4678-8).
 23. Mazidi M, Karimi E, Rezaie P, Ferns GA. Treatment with GLP1 receptor agonists reduce serum CRP concentrations in patients with type 2 diabetes mellitus: a systematic review and meta-analysis of randomized controlled trials. *J Diabetes Complications*. 2017;31(7):1237-42. doi: [10.1016/j.jdiacomp.2016.05.022](https://doi.org/10.1016/j.jdiacomp.2016.05.022).
 24. Atalar MN, Abuşoğlu S, Ünlü A, Tok O, İpekçi SH, Baldane S, et al. Assessment of serum galectin-3, methylated arginine and Hs-CRP levels in type 2 diabetes and prediabetes. *Life Sci*. 2019;231:116577. doi: [10.1016/j.lfs.2019.116577](https://doi.org/10.1016/j.lfs.2019.116577).
 25. Heidarianpour A, Keshvari M. Effects of three types of exercise aerobic, resistance and concurrent on plasma CRP concentration in type II diabetes patients. *J Sabzevar Univ Med Sci*. 2016;23(6):916-25. [Persian].
 26. Bashardoust B, Alaei R, Mohammadi Kebar S, Hasani S, Habibzadeh A. The effect of oral N-acetylcysteine on serum high sensitive CRP and plasma hemoglobin levels in end-stage renal disease patients under routine hemodialysis; a randomized placebo-controlled clinical trial. *J Nephropathol*. 2018;7(4):268-72. doi: [10.15171/jnp.2018.53](https://doi.org/10.15171/jnp.2018.53).
 27. Shahbazian H, Shayanpour S, Ghorbani A. Evaluation of administration of oral N-acetylcysteine to reduce oxidative stress in chronic hemodialysis patients: a double-blind, randomized, controlled clinical trial. *Saudi J Kidney Dis Transpl*. 2016;27(1):88-93. doi: [10.4103/1319-2442.174084](https://doi.org/10.4103/1319-2442.174084).
 28. Giannikouris I. The effect of N-acetylcysteine on oxidative serum biomarkers of hemodialysis patients. *Hippokratia*. 2015;19(2):131-5.