

Original Article



The effect of eight weeks of high-intensity interval training with L-cysteine consumption on interleukin-13 and oxidative stress of heart tissue in young rats with type 2 diabetes

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Abstract

Background and aims: The purpose of this study was to investigate the effect of 8-weeks of high-intensity interval exercise with L-cysteine (LC) consumption on *interleukin* (IL)-13 and hydrogen peroxide of the heart tissue in young rats with type 2 diabetes (T2D).

Methods: The statistical population of the present study consisted of young (4-month) rats with T2D. Ten rats were selected as a healthy group. Forty rats became diabetic. Diabetic rats were randomly divided into diabetes control, diabetics with exercise, diabetics with supplements, and diabetics with exercise and supplements. High-intensity interval exercises were performed 3 days a week for 8 weeks, and 500 µmol of LC were injected daily.

Results: The healthy control group had lower IL-13 than the control group ($P=0.001$). There was no significant difference in IL-13 between other groups. Based on the results, the diabetes control group had a higher H_2O_2 value than the healthy control group ($P=0.001$). A significant difference was found between the exercise group+LC consumption compared to the diabetes control group, and the H_2O_2 levels in this group were less than the diabetic control group ($P=0.001$). The exercise ($P=0.015$) and LC ($P=0.001$) groups had a lower H_2O_2 value than the diabetes control group. Eventually, the interval exercise group+LC was also lower than the periodic exercise group ($P=0.02$).

Conclusion: High-intensity interval training, along with the use of LC, reduced hydrogen peroxide in the heart tissue, while it had no significant impact on IL-13.

Keywords: Type 2 diabetes, IL-13, Oxidative stress, L-cysteine

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Introduction

Type 2 diabetes (T2D) is currently one of the most common diseases, and its patients are gradually increasing (1). More than 50% of people with diabetes die due to cardiovascular disease (mainly heart disease and stroke), and the only cause of kidney disease is the final stage which requires dialysis or kidney transplantation. In this regard, it has been shown that diabetes is associated with increased oxidation pressure (2). The high concentration of free radicals results in harmful processes that can damage cellular structures due to oxidative stress (OS) (3). OS is also highly involved in insulin resistance caused by chronic hyperglycemia (4). Chronic hyperglycemia has been reported as a major factor in the development of microvascular complications in T2D. Also, hyperglycemia has been shown to be responsible for DNA damage, damage to lipids and proteins, and oxidative stress (4). In addition, the spread of inflammatory intermediaries is due to the high concentration of glucose and OS (5).

Chronic inflammation and OS are involved in the pathophysiology of diabetes. Inflammation and OS in physiological and disease states are integrated separately (5). Chronic inflammation causes its cellular side effects

mainly through the continuous production of free radicals and reduced antioxidants (6). Experimental evidence in mice has demonstrated that *interleukin* (IL)-13 may also participate in systemic inflammation and insulin resistance (7). In this regard, exogenous IL-13 has been reported to improve insulin sensitivity while decreasing tumor necrosis factor- α (TNF- α) and macrophages in the adipose tissue of epididymal C57BL/6J mice fed a high-fat diet (8). Interestingly, IL-13 is also associated with improving insulin secretion. In this respect, Darkhal et al found that excessive expression of the *IL-13* gene corresponds to an increased level of insulin in mice (9).

It seems that using proper dietary supplements and exercise can be effective in reducing the complications of diabetes. Cysteine is an amino acid with the formula ($Sch_2ch(NH_2)Co_2h$), which is produced in the human body by the oxidation of two cysteine molecules that form a disulfide bond (10). L-cysteine (LC) is a cellular glutathione precursor that plays a key role in detoxifying cellular OS (20). LC supplements can improve blood sugar or vascular inflammation in normal or diabetic models (11). Diabetic patients have lower blood levels of LC and H_2S , as well as altered cysteine homeostasis (12). Other

studies have also represented that LC supplements reduce OS markers in T2D patients and normal individuals (13). The results have also revealed that feeding with LC and NA2S reduces *nuclear factor-κB* phosphorylation and the secretion of TNF-α, *monocyte chemoattractant protein-1*, IL-8, IL-1β, and IP-10 (14).

On the other hand, lifestyle and environmental factors have been reported as the main causes of a sharp increase in the incidence of T2D (15). Cross-sectional, futuristic, and retainer studies have found a significant relationship between physical inactivity and T2D (16). During a long session of physical activity, skeletal muscle contraction increases glucose absorption in cells. This effect increases blood flow to the muscle and increases the transfer of glucose into muscle cells (15). Unlike intense short-term exercise, chronic and long-term exercise has the effects of reducing inflammation and OS (16). However, little research has been performed on the effects of exercise on IL-13. Tucker et al indicated that practiced women had significantly higher IL-13 expressions than low-income women (17). Nabilpour and Sadeghi examined the effect of eight weeks of medium-intensity aerobic continuous exercise on the levels of IL-1 and IL-13 in the male tissue of the diabetic model, but no significant change was observed in IL-13 (18). On the effect of exercise on oxidation in diabetic patients, Man et al concluded that exercise reduces oxidation and improves vascular function (19). A combination of exercise and supplements with antioxidant and anti-inflammatory content such as LC leads to better results in reducing inflammation and oxidation, but no clear results have been provided in this regard.

Moreover, interval training programs are superior to improving metabolic parameters compared to continuous exercise diets, or high-level improvements but less exercise volume. In this regard, some researches have shown that interval aerobic walking exercises compared to continuous walking exercises have similar or better effects for improving body composition, fitness and blood glucose control in patients with type 2 diabetes.(20,21). In addition, chronic and long-term exercise is effective in reducing OS and inflammation (16). Therefore, the present study sought to evaluate the effect of 8 weeks of high-intensity interval training with LC consumption on IL-13 and oxidation stress of young rats with T2D.

Materials and Methods

The statistical population of this experimental study was composed of young (4-month) diabetes mice. Totally, 50 rats were purchased from one of the research centers and then placed in laboratory conditions with free access to water and food and 24:12 laboratory conditions (12:12). Next, a number of diabetic rats became diabetic. A single dose of streptozotocin (STZ) was used and given to diabetic mice. Induction of diabetes was done intravenously with a single dose of 50 mg/kg STZ, and blood sugar above 250 mg/kg, 1 week after injection, was considered induced

diabetes. Subsequently, mice in the field were divided into five groups, including healthy control, diabetes control, diabetics with exercise, diabetics with supplements, and diabetics with exercise and supplements. High-intensity periodic exercises were performed 3 days a week. Supplements were also injected into the rats. After all the training and supplementation, the rats were anesthetized and the heart was extracted 48 hours later.

Planning of correction and frequency

- Health control (10 rats): In this grade, the halls were not the same as all three of them in the form.
- Diabetes control (10 rats): This group became diabetic with a diabetic peritoneum with a single dose of 50 mg/kg STZ .
- Diabetic with exercise (10 rats): This group became diabetic intravenously with a single dose of 50 mg/kg STZ, and then the interval exercise was performed on the 5th day.
- Diabetic with supplements (10 rats): This group was dissolved by a single dose of 50 mg/kg STZ and 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 μmol).
- Diabetic with exercise and supplement (10 rats): This group was on an intra-peritoneal diet with a single dose of 50 mg/kg STZ and then participated in interval exercise for 6 weeks, and 1/5 pills (200 mg; Hexal; Germany (3 mL of water was dissolved and 500 micro mols were soluble daily.

Interval training protocol

The high-intensity interval training protocol included 10 bouts of 2-minute high-intensity running on a treadmill with 90% of VO_{2max} with 60-second rest at a speed of 20 m/minute in the first week, and the speed was gradually increased to 30 m/minute in the 8th week (no slope). Warming and cooling down time was 5 minutes (22), the details of which are provided in Table 1.

L-cysteine-consuming Protocol

For this purpose, 1.5 LC tablets (200 mg; Hexal; Germany) were dissolved in 3 mL of water and a 500 μM daily given soluble. The dose of LC- was proportional to the dose of the human being and was calculated based on the formula of human to animal (23).

Sampling was performed 48 hours after the last training session and after a fasting night. To collect samples, first, the mouse was anesthetized with a combination of xylazine (10 mg/kg) and ketamine (100 mg/kg) into intra-peritoneal injection. Then, the heart of the mice was extracted, and after washing in the physiological serum, it was immediately frozen in liquid nitrogen and maintained for molecular cell tests in a freezer of -80 °C.

Enzyme-linked immunosorbent assaytesting method

The Level of IL-13 was assayed in the heart tissue lysate

sample by the RayBio® Rat IL-13 ELISA Kit (Catalog #: ELR-IL13-CL) The hydrogen peroxide review of the Fluorimetric Hydrogen Peroxide Assay Kit was employed for the MAK165 Catalog Number Sigma-Aldrich.

Statistical methods

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

Results

Table 2 presents data on body weight. Body weight in the diabetes control group increased significantly compared to the healthy group ($P=0.02$). Conversely, there was a significant decrease in the exercise group with supplements compared to the diabetes control group ($P=0.04$). However, no significant change was observed in body weight in the exercise ($P=0.053$) and supplement ($P=0.051$) groups in comparison to the diabetes control group.

The results of the ANOVA statistical test demonstrated that there was a significant difference between the groups in terms of the amount of IL-13 in the heart tissue ($P=0.001$, Table 2). The Bonferroni post hoc test also revealed that the healthy control group had a significant amount of IL-13 than the diabetic control group ($P=0.001$). Contrarily, interval exercise ($P=0.99$) and LC ($P=0.19$) alone and interval exercise+LC ($P=0.089$), compared to the diabetes control group, had no significant effect on IL-13 heart tissue levels (Figure 1).

Based on ANOVA statistical test results, a significant difference was found between the groups in terms of H_2O_2 ($P=0.001$, Table 1). The Bonferroni post hoc test also showed that the diabetes control group had a higher H_2O_2 value than the healthy control group ($P=0.001$). There was a significant difference between the exercise group+LC consumption compared to the diabetes control group, and the H_2O_2 levels in this group were less than the diabetic control group ($P=0.001$). The exercise group ($P=0.015$) and the LC group ($P=0.001$) had a lower H_2O_2 value than the diabetes control group. The interval exercise group+LC was also lower than the periodic exercise group ($P=0.02$, Figure 2).

Discussion

Our results on hydrogen peroxide represented that diabetes control groups have a higher H_2O_2 value than the healthy control group. Asmat et al (24) and Zhang et al (25) also reported similar results. OS is believed to play an important role in causing vascular complications in diabetes, especially T2D (24). Increased reactive oxygen species (ROS) levels in diabetes may be due to decreased degrees or/and increased production by catalase

Table 1. HIIT 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 Group.

Groups	Mean ± SD
Health control	215 ± 15
Diabetic control	273 ± 12
Training	251 ± 8
Supplement	244 ± 8
Training+supplement	233 ± 8

Note. SD: Standard deviation.

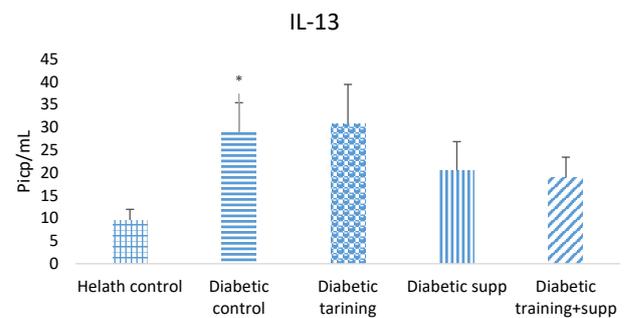


Figure 1. IL-13 in All Groups. Note. IL: Interleukin. * Significant difference with health control

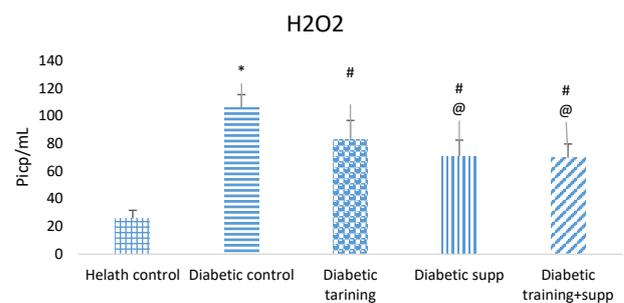


Figure 2. H_2O_2 in All Groups. Note. * Significant difference with health control; # Significant difference with diabetic control; @ Significant difference with diabetic training

antioxidants (CAT-enzymatic/non-enzyme), superoxide dismutase (SOD), and glutathione peroxidase. Diversity in the levels of these enzymes makes tissues susceptible to OS, leading to diabetes complications (24). According to epidemiological studies, diabetes-related mortality can be significantly explained by increasing vascular diseases other than hyperglycemia (24).

In this study, LC and interval exercise alone had a significant impact on hydrogen peroxide in the heart tissue of diabetics, and in interaction with each other,

it significantly reduced H₂O₂. Salman et al also found that LC reduces oxidation pressure in T2D (26). Dłudla et al reported similar results in this regard (27). LC, a glutathione precursor, can fill all the hybrid thiols (cysteine, cysteine glycerin, glutathione, and homocysteine), interact with ROS electrophiles, and then increase total antioxidant capacity (28). Previous studies indicated the potential N-acetylcysteine (NAC) antioxidant, anti-inflammatory, and potential properties in *chronic obstructive pulmonary disease* (COPD). Adding NAC to COPD standard treatment has shown beneficial effects on exacerbation, improved symptoms, and reduced OS parameters (28). Some studies represented that NAC increases manganese-SOD protein and mRNA without altering the mRNA expression of other antioxidant enzymes, including glutathione peroxidase 1, copper/zinc-SOD, and extracellular SOD (28).

Our results in terms of the impact of exercise are in line with the findings of Afrundeh et al (29) and Hafezi et al (30). Increasing antioxidant enzyme activity due to exercise, including SOD and CAT, is effective in reducing oxidation pressure due to exercise (2,31). However, no clear results have been reported on the effect of exercise and LC. Interval exercise and consumption of LC appear to be effective in reducing oxidation by increasing antioxidant enzymes.

Moreover, research on IL-13 in the heart tissue demonstrated that the diabetes control group had a significant amount of IL-13 than the healthy control group. Martinez et al also concluded that IL-13 levels increased in people with insulin resistance but with low-degree systemic inflammatory markers (7). The serum levels of IL-13 in type 2 diabetic patients with coronary artery disease decreased compared to healthy people (32). In contrast, it was also found that obese patients with insulin resistance have higher amounts of serum IL-13 than the normal weight control group and reduce the semester level of IL-13 after 1 year of surgery (33). This contradiction can be attributed to the potential role of IL-13 in the pathogenesis of insulin resistance, affecting the liver, adipose tissue, skeletal muscles, and beta-pancreatic cells. In this regard, a previous study on mice showed that the deficiency of the *IL-13* gene was associated with reduced insulin receptor substrate-1 and protein kinase B phosphorylation in the liver, adipose tissue, and skeletal muscles, which is directly associated with reduced insulin sensitivity in the above-mentioned tissues (34).

The findings of another study revealed that the expression of the *IL-13* gene tends to increase in the free ventricle wall of T2D patients with heart failure compared to healthy donors (35). Interestingly, although the *IL-13* gene tended to adjust positively, the production of alpha 1 IL-13 (IL-13R α 1) subdivision (IL-13R α 1) is significant in the same heart muscle samples of T2D patients with heart failure, which decreased according to Are insulin resistant (35). To some extent, these results are in line with

our findings and indicate the gradual loss of cell capacity to respond to IL-13 in the insulin resistance scenario. Such an "IL-13" resistance may partially explain the serum level of IL-13 in several groups of patients with insulin resistance, including our studied population.

Similarly, our results demonstrated that interval exercise and the use of LC did not make a significant change in IL-13. Nabilpour and Sadeghi also examined the effect of eight weeks of medium-intensity aerobic continuous exercises on the IL-1 and IL-13 levels of the male muscle tissue of the diabetic model but reported no significant change in IL-13 (18). IL-13 is a cytokine, which is produced during type 2 immune responses, contributing to safety and many other allergic inflammatory diseases. It also induces specific effects on the immune system and is capable of deactivating the type 1 T helper (TH1) or an inflammatory macrophage response. IL-13 also results in a negative adjustment of the production of pro-inflammatory monocyte/macrophage, including active oxygen species and nitrogen intermediaries (19). There are no clear results on the effect of LC alone or in interacting with exercise on IL-13. However, it seems that LC is effective in increasing IL-13 by reducing oxidation and inflammatory cytokines. Considering that LC reduces insulin resistance (36) and reduced insulin resistance is effective in reducing oxidation, oxidation changes are effective at IL-13 levels.

Conclusion

Based on the findings, high-intensity interval training, along with the use of LC, reduced hydrogen peroxide in the heart tissue. However, it had no significant impact on IL-1.3.

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Authors' Contribution

Conceptualization: Mana Davoudi.

Data curation: Mana Davoudi, Akbar Nouri Habashi.

Methodology: Mana Davoudi.

Project administration: Akbar Nouri Habashi.

Supervision: Akbar Nouri Habashi.

Writing—original draft: Mana Davoudi.

Writing—review & editing: Akbar Nouri Habashi.

Competing Interests

The authors have no conflict of interests.

Ethical Approval

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

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