The Efficacy of Home-based Resistance Exercise and Game-based Exercise Training on microRNA-21-5p Expression and Non-Alcoholic Fatty Liver Biomarkers in Children with Type 1 Diabetes

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Abstract

Background: At present, increasing evidence has reported circulating microRNAs (miRNAs) as potential clinical biomarkers for specific diseases and administration of pharmaceutical agents. The main aim of this study was to compare the effect of two selected home-based resistance exercise (HBRE) and game-based exercise training (GBET) groups on microRNA21-5p expression and biomarkers related to non-alcoholic fatty liver in children with type 1 diabetes (T1D).

Materials and Methods: Twenty children with T1D aged 10–15 years were randomly assigned to one of two groups (HBRE: n = 10; GBET: n = 10). The exercise training lasted for 8 weeks with three sessions per week. The liver enzyme profile, hemoglobin A1c (HbA1c), glucose, microRNA-21-5p, insulin, and Homeostasis Model Assessment for Insulin Resistance (HOMA-IR) levels were measured before and after the interventions in both groups. In addition, the cardiopulmonary fitness and body fat percentage (BF%) of the participants were also evaluated.

Results: After exercise interventions, miR-21-5p increased significantly for both intervention groups (HBRE: 8.9% vs. GBET: 6.7%; $P = 0.001$). The levels of alanine transaminase (ALT) (HBRE: 60.71% vs. GBET: 49.15%) and aspartate aminotransferase (AST) enzymes (HBRE: 54.02% vs. GBET: 34.02%), the glucose (HBRE: 15.03% vs. GBET: 16.26%), and the HbA1c (HBRE: -10.44% vs. GBET: -6.52%) were decreased significantly ($P \leq 0.05$). The cardiorespiratory endurance of subjects increased (HBRE: 2.85% vs. GBET: 3.75%), but there were no differences between groups ($P \geq 0.05$).

Conclusions: Both HBRE and GBET protocols were effective to improve cardiorespiratory fitness, liver enzyme profile, glycemic control, and miR-21-5p changes that seem to be indicative of the pathological status of T1D children.

Keywords: Adolescent, biomarkers, diabetes mellitus, exercise, MicroRNAs, non-alcoholic fatty liver disease, type 1

INTRODUCTION

Along with the increasing prevalence of type 1 diabetes (T1D), there has been a growing concern about its associated comorbidities, such as fatty liver disease.[1] Fatty liver disease, also known as non-alcoholic fatty liver disease (NAFLD), is a common liver condition that affects individuals with T1D and obesity. NAFLD is characterized by the accumulation of fat in the liver, which can lead to inflammation, scarring, and liver damage.[2] The relationship between T1D and NAFLD

is complex and not yet fully understood. However, recent research has shed light on the mechanisms underlying the development of NAFLD in individuals with T1D.[3]

Results of different studies about the prevalence of NAFLD in patients with T1D are not similar, and some reported a higher rate of fatty liver in this population compared to individuals without T1D.[4] The exact mechanisms underlying the development of fatty liver disease in T1D are not yet fully understood, but several factors have been implicated.[2] Studies have shown that poor glycemic control, longer duration of T1D, and obesity are associated with an increased risk of developing fatty liver disease in patients with T1D.[5] Longer duration of T1D is also associated with an increased risk of fatty liver disease, possibly due to the cumulative effect of chronic hyperglycemia and insulin resistance.[4] Obesity is a well-established risk factor for cardiovascular problems and fatty liver disease, and its prevalence is particularly high in patients with T1D who are overweight/obese.[6] Studies have shown that lifestyle interventions, better glycemic control, and exercise training can prevent and manage fatty liver disease in patients with T1D.[7] However, physical exercise can be difficult due to glycemic disturbances and hypoglycemia risk, which are major barriers. Adolescents with T1D face these diabetes-specific challenges in addition to common physical exercise barriers.

Physical exercise can reduce liver fat and improve liver function in T1D patients.[8] Physical activity may impact NAFLD prevention and treatment by affecting mitochondrial function and structure. However, the roles of microRNAs (miRNAs), DNA methylation, and histone modification in NAFLD development remain unclear and require further investigation.[8]

Recent research has examined the involvement of miRNAs in the development and progression of NAFLD in children. Dysregulation of miR-122, miR-34a, miR-21, and miR-192 has been observed in children with NAFLD, suggesting their potential role in regulating lipid metabolism, inflammation, and fibrosis in the liver. Targeting these miRNAs could be a potential therapeutic approach for treating NAFLD in children.[8] However, further research is needed to validate their use as diagnostic and therapeutic tools.

The increasing incidence of T1D and its related complications emphasizes the need for effective interventions to prevent or manage these conditions. Physical exercise has shown promise in preventing and managing fatty liver disease, a common comorbidity in T1D patients. Noninvasive diagnostic markers, such as miRNAs, are dysregulated in patients with NAFLD, indicating their potential use as diagnostic and therapeutic tools.[8]

Considering that both home-based resistance exercise (HBRE) and game-based exercise training (GBET) protocols could overcome key barriers to exercise in adolescents with T1D. This study aims to investigate the effect of two selected HBRE and GBET groups on miR-21-a level and biomarkers related to non-alcoholic fatty liver in children with T1D. The research seeks to determine whether changes in miRNA levels due to exercise interventions can serve as biomarkers to predict future non-communicable disease risks in adulthood. The study could provide valuable insights into the benefits of physical exercise and miRNA evaluation for high-risk populations, such as T1D children and adolescents.

MATERIALS AND METHODS

Design and population

This study was designed as a randomized controlled trial with a pretest-posttest design that was held in Isfahan, Iran. T1D patients aged 10–15 years referred to diabetes clinics of Isfahan City were enrolled in the study. The exclusion criteria for participants were as follows: (1) voluntary withdrawal of participants for any reason; (2) illness and injury or inability to exercise during the research period; and (3) absence of more than three sessions during the training period. The Consolidated Standards of Reporting Trials (CONSORT) diagram of participants' recruitment, allocation, and analysis is indicated in Figure 1. The consent form was obtained from parents and students before the start of the course. Selected were randomly assigned to two groups: HBRE (n = 10) and GBET (n = 10).

Before the training sessions, all selected patients with T1D and their parents were informed about the details of the training sessions and the protocol. They were also trained on how to achieve better glycemic control before, during, and after the training sessions, based on the recommended guidelines for exercise in children with T1D.

This comprehensive training ensured that both the participants and their parents were fully informed about the structure, objectives,
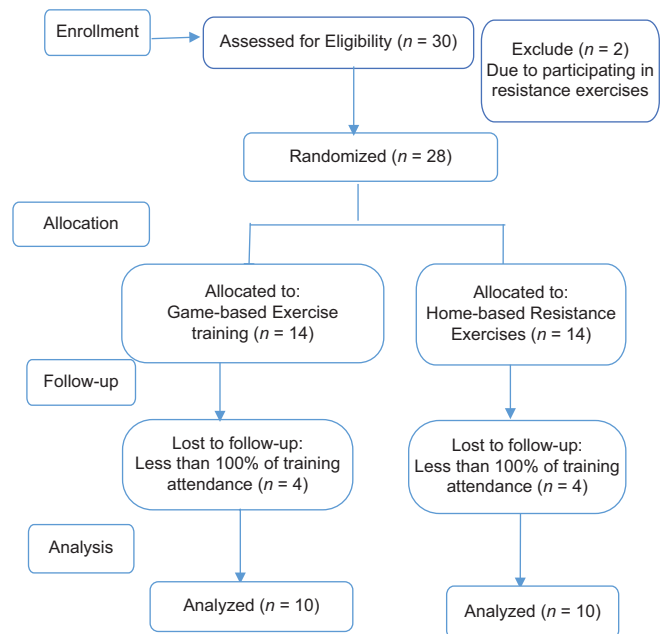

Figure 1: CONSORT flow chart of participants for recruitment, application, follow-up, and analysis

and proper execution of the training program. The training was conducted in accordance with the established guidelines for exercise management in pediatric T1D populations.[8]

The goal was to equip the patients and their parents with the necessary knowledge and skills to effectively manage the patients' glycemic levels throughout the training sessions, in order to optimize the safety and benefits of the exercise program.

To make sure that the effect of the exercise interventions was less affected by other covariate variables, participants and their parents were instructed to maintain their regular diet and daily physical activity during the exercise intervention periods.

Measurements
Anthropometric measurements
Participants' body weight and height were assessed at baseline. The body mass index (BMI) was calculated by dividing the weight by the square of the height in meters. Body fat percentage (BF%) was determined using a body composition analyzer (InBody 270, Korea).[9] The peak oxygen uptake (VO$_2$peak) was assessed by the 20-m multistage shuttle run test using the standard procedure. The total number of laps has been used to estimate peak oxygen consumption (VO$_2$peak), using the formula proposed by Matsuzaka *et al.*[10]

Biochemical measurements
The extraction of serum and biochemical measurements
The blood samples containing 5cc following 12 hours of overnight fasting in pretest-posttest phases (24 hours before and 48 hours after the last training session) were collected from the left brachial vein in the sitting position and transferred to test tubes. The blood samples were centrifuged at 4°C for 10 minutes at a speed of 3000 RPM, and the resulting serums were frozen at -80°C until further measurements of fasting blood sugar (FBS), hemoglobin A1c (HbA1c), liver function tests, and insulin levels.

The diagnostic kits of Pars Azmoon (Tehran, Iran) were used for the measurement of FBS and alkaline phosphatase (ALP) and aspartate aminotransferase (AST) liver enzymes. HbA1c levels were measured using the high-performance liquid chromatography (HPLC) method with Labnovation LD-600 equipment (China). Insulin resistance was calculated by three formulas as follows: Homeostasis Model Assessment for Insulin Resistance (HOMA-IR) = (fasting plasma glucose level [mg/dL] × fasting insulin level [μunit/mL])/405.[11]

The measurement of serum miR-21-a
The reverse transcription-quantitative polymerase chain reaction (RT-qPCR) method was applied to measure the serum level of miRNA-21-a. To this end, miRNA was first extracted from serum samples by PAXgene Blood miRNA Kit (Qiagen, Germany) based on the method provided by the manufacturer. cDNA Synthesis Kit was used for RT of the extracted RNAs based on the manufacturer's recommended protocols. Then, the human miRNA-21-a sequence was extracted from the miRBase database and the desired primer was designed by

the web-based software miRNA design tool to perform RT and qPCR. The processes of RT and qPCR were conducted using the kit prepared by Ansal Company (Tehran, Iran), including primer sequences and SYBR Green-based Master Mix. In this study, U6 was considered a control gene. RT was performed according to the technique provided by the kit, and qPCR was performed using Rotor-Gene 6000 (Corvette, Australia) during 40 two-stage cycles including 30 seconds at 95 degrees and 30 seconds at 60 degrees. The melting test was conducted at 65 to 95 degrees in 1-degree increments. The findings were analyzed by the REST software to calculate the relative expression (fold change) for each candidate miRNA within each group and were then calculated using the equation: $2^{-\Delta\Delta Ct}$.[12,13] The results were represented based on the Δ ct of pretest and posttest of each group as well as their fold changes.

Exercise interventions
Resistance exercises were performed three times a week and were designed as HBRE, so the resistance was human body weight. Values for intensity, duration, and effort gains in the HBRE group were closely monitored.[14] To do this, subjects performed their exercises under the guidance of a researcher once a week, while they recorded their activities in home sessions (twice a week). The videos were sent weekly to the research team. Table 1 summarizes the exercise program of the HBRT group.[15] In the GBET group, subjects were required to participate in their leisure activities, such as soccer, cycling, volleyball, swimming, and gymnastics, 3 days a week, for a total of 150 minutes of regular exercise per week.[16] Practicing basic sports skills and playing games starts with 50 minutes in the first week, increasing by 5 minutes every 2 weeks and about 75 minutes in the final training. Each session included 15 minutes of warm-up and cool-down exercises.

As mentioned above, all patients and their parents were trained on how to achieve better glycemic control before, during, and after the training sessions, based on the recommended guidelines for exercise in children with T1D.

Statistical analysis
To calculate the mean and standard deviation values of the variables, descriptive statistics were used. The Shapiro-Wilk test was used to determine the normality of the data. To determine the effects of the intervention, analysis of covariance (ANCOVA) test was used, with the changes in miR-21-a, liver enzymes, VO$_2$peak as the dependent variables, and baseline data of miR-21-a, lipid liver enzymes, VO$_2$ peak, and BF% as the covariates. The IBM SPSS software version 22 (IBM, Armonk, New York, USA) was used for the analysis of data. The significance level was set at $P \leq 0.05$.

RESULTS

Twenty adolescents, both boys and girls, participated in the study. The mean ages of participants in the HBRE and GBET groups were 12.6 (±1.3) and 12.4 (±0.8) years, respectively.

The two study groups were matched for age and sex [in the HBRE group: female/male = 6/4; in the GBET group: female/male = 7/3 (*P* > 0.05)]. The characteristics of the participants in the two studied groups at baseline and after the training period are presented in Table 2.

At baseline (pretest), participants in both groups were similar in terms of weight, BMI, percentage of body fat, and VO₂ peak (*P* > 0.05). The mean levels of biochemical variables of participants at baseline and posttest are shown in Table 3. The mean level of ALT, AST, glucose, HbA1c, and miR-21-a has a significant change after the training period in the two studied groups (*P* < 0.05). The mean level of HOMA-IR had no significant change after training sessions (*P* < 0.05). The insulin level increased significantly in the GBET group after training (*P* < 0.05).

As shown in Figure 2, miR-21-a levels were significantly changed in the HBRE and GBET groups after intervention (within-group variability) (HBRE: 8.9% vs. GBET: 9.2%; *P* = 0.012;

η2 = 0.228), but no significant differences were observed between the two experimental groups (*P* = 0.513; η2 = 0.118).

Discussion

This study aimed to investigate the effects of two selected exercise modes, HBRT and GBET, on the levels of miR21-a, liver enzymes, fasting blood sugar, insulin, and insulin resistance in adolescents with T1D. The results showed a slight but significant increase in miR-21a levels after 8 weeks of exercise interventions in both HBRT and GBET groups after training. However, there was no significant difference between the two exercise groups. We also found a significant decrease in the level of liver enzymes, HbA1c, and glucose levels in both groups after the intervention, but there were no significant differences between the two types of exercises. The insulin resistance had no significant change after interventions in both groups.

The results of our study regarding the effectiveness of the two types of training on the expression of miR-21-5p and glycemic control are consistent with Valenti *et al*.,[17] Zhou *et al*.,[12] Aljawarneh *et al*.,[18] and García-Hermoso *et al*.[19] but not with Nielsen *et al*.[20] and Liu *et al*.[21]

Table 1: Summary of the training program for the HBRT group

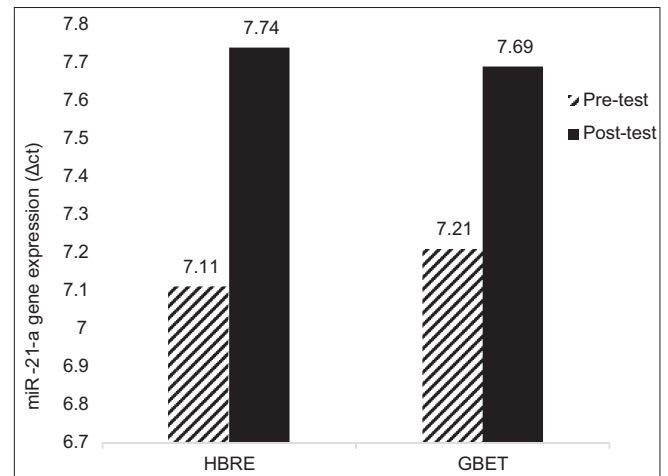| Exercises	Repetitions/time	Sets	Rest time
Standing half squat	15 REPs	2	40 SECs
Russian twist	15 REPs	2	40 SECs
Mountain climber	20 REPs	2	40 SECs
Butt lift–bridge	15 REPs	2	40 SECs
Push up	10 REPs	2	40 SECs
Bicycle crunches	20 REPs	2	40 SECs
Plank	20 REPs	2	40 SECs
Sicilian crunch	15 REPs	2	40 SECs
Lunge	15 REPs	2	40 SECs
Breaststroke straighten back	20 SECs	2	40 SECs
Donkey kick left	10 REPs (with each leg)	2	40 SECs
Crunch toe touch	15 SECs	2	40 SECs
Side leg lift right	15 REPs	2	40 SECs
Side leg lift left	15 REPs	2	40 SECs
Side plank	15 SECs (on each hand)	2	40 SECs

REPs: repetitions, SECs: seconds

Figure 2: Mean miR-21a values in the two studied groups at baseline and after training. HBRE: home-based resistance exercise, GBET: game-based exercise training

Table 2: Characteristics of the participants in the two studied groups at baseline and after the training period

Variables	Groups	Pretest	Posttest	*P* (pre-post)	*P* (between groups)
Weight (Kg)	HBRE (*n*=10)	45.3±11.9	45.8±12.49	*P*=0.12	*P*=0.024#
	GBET (*n*=10)	51.9±13.2	51.0±12.8	*P*=0.14	
BMI (Kg/m²)	HBRE (*n*=10)	18.2±4.0	18.3±3.8*	*P*=0.007	*P*=0.589
	GBET (*n*=10)	20.7±3.6	20.2±3.7*	*P*=0.001	
BF (%)	HBRE (*n*=10)	24.1±8.7	24.4±8.5	0.407	*P*=0.779
	GBET (*n*=10)	26.7±8.2	27.0±8.2	0.332	
CRE (ml/kg⁻¹.min⁻¹)	HBRE (*n*=10)	42.3±3.6	43.3±3.8*	*P*=0.001	*P*=0.063#
	GBET (*n*=10)	39.7±3.7	41.2±4.2*	*P*=0.001	

Mean±SD (*P*<0.05). *differences between time points within the conditions (pre-post), #differences between experimental groups, CRE: cardiorespiratory endurance, ml/kg⁻¹.min⁻¹: milliliters per minute per kilogram of body mass; HBRE: home-based resistance exercise, GBET: game-based exercise training; BMI: body mass index; BF: body fat

Table 3: Mean±SD of biochemical measurements in the two studied groups at baseline and after the training period

Variables	Groups	Pretest	Posttest	Δ (%)	CI 95% for the difference	*P* Time(pre-post)	*P* Between groups
miR-21-5p (ΔCt)	HBRE	7.11±0.8	7.74±0.6*	8.9	[7.5; 8.1]	0.009	
	GBET	7.21±0.9	7.69±1.0*	9.2	[7.3; 7.9]	0.005	0.513
ALT (mg/dl)	HBRE	9.0±4.2	5.6±2.0*	60.7	[6.7; 11.6]	0.013	
	GBET	8.8±4.3	5.9±2.9*	49.2	[6.2; 11.1]	0.036	0.342
AST (mg/dl)	HBRE	13.4±2.5	8.7±2.1*	54.0	[12.2; 15.2]	0.001	
	GBET	13.0±2.8	9.7±3.2*	34.0	[11.2; 14.2]	0.004	0.342
HbA1c (%)	HBRE	9.19±2.2	8.23±1.9*	-10.4	[7. 89; 8.57]	0.010	
	GBET	9.2±1.3	8.16±1.4*	-6.5	[8. 25; 8.93]	0.007	0.133
Insulin (μU)	HBRE	0.795±0.5	1.098±0.4	38.1	[0.495; 1.72]	0.240	
	GBET	0.820±0.5	1.298±1.3*	58.3	[0.677; 1.90]	0.009	0.663
HOMA-IR	HBRE	0.524±0.5	0.584±0.3	11. 5	[0.341; 0.769]	0.566	
	GBET	0.417±0.3	0.522±0.4	25.2	[0.339; 0.766]	0.402	0.985
Glucose (mg/dl)	HBRE	244.7±83.6	207.9±78.8*	-15.0	[173.7; 219.9]	0.006	0.755
	GBET	215.8±66.1	180.7±52.3*	-16.3	[168.7; 214.9]	0.027	

Data are mean±SD; *P*<0.05, *differences between time points within the conditions, Δ (%): percentage of change between initial and final measurements, HBRE: home-based resistance exercise, GBET: game-based exercise training; HbA1c: glycated hemoglobin, HOMA-IR: Homeostasis Model Assessment for Insulin Resistance, ALT: alanine transaminase, AST: aspartate aminotransferase; ΔCt: the difference of expression between two genes, mg/dl: milligrams per deciliter; CI: confidence interval

Vandoni and colleagues found that miR-21a decreased after 12 weeks of resistance training in athletes, indicating that changes in miR-21a depend on the type and intensity of training. Endurance athletes have higher baseline levels than strength athletes.[22] Studies have shown that miR-21 has multiple functions, such as activating T cells and regulating immune and anti-inflammatory responses, as well as dual effects on pancreatic beta cells, and may have different changes in T1D patients at different stages.

MiR-21 has also been shown to be involved in regulating cell death of pancreatic beta cells and insulin secretion stimulation. MiR-21 is known as one of the accessible miRNAs in the cardiovascular system, and previous studies have demonstrated important characteristics of miR-21 in the cardiovascular system with assays showing increased mutations and loss of function. However, miR-21 expression patterns and functions reported in different CVDs are different.[12] Considering our findings, it is suggested that physical activity could prevent the development of T1D-related complications, such as NAFLD and cardiovascular complications, through modulation of function and structure of mitochondria as well as other epigenetic mechanisms, including the role of miRNAs, DNA methylation, and histone modification.[23]

It has been shown that there was a significant decrease in ALT enzyme levels compared to the pretest in the selected HBRE (60.71%) and GBET (49.15%) groups after 8 weeks of exercise interventions. However, no significant difference was observed between the two training groups. Regarding AST enzyme levels, we also found a significant decrease compared to the pretest in the selected HBRE (54.02%) and GBET (34.02%) groups after 8 weeks of exercise interventions. Results of a systematic review and meta-analysis by Babu *et al*. have demonstrated that exercise without substantial weight loss was found to significantly decrease the concentrations of ALT and AST.[24] Zinvand Lorestani *et al*. reported significant reduction in the level of the liver enzymes after 12 weeks of aerobic exercise in obese children.[25]

Results of a recent systematic review and meta-analysis regarding the effectiveness of different types of exercise on key indicator of NAFLD found that aerobic training is the most effective mode of exercise for improving ALT and resistance training is the optimal exercise modality for improving AST. They concluded that by considering the various benefits observed, the best exercise approach for patients with NAFLD is a combination of aerobic training and resistance training.[26]

Recent studies suggest that the prevalence of NAFLD in T1D is high, but there is significant variability in current studies due to differences in diagnostic accuracy, retrospective study designs, and other factors, such as metabolic control and patient education.[2] Elevated liver enzymes are considered a risk factor for developing NAFLD and its related comorbidities in T1D patients. Therefore, it is recommended that exercise training programs be implemented into the daily routine of patients to help prevent T1D-related complications.[27]

Based on the findings of recent studies, it is suggested that miRNAs may play a vital role in the development of NAFLD and its progression to more severe forms and that targeting these miRNAs could be a potential therapeutic approach for treating the disease.[28,29] However, further research is needed to validate the use of miRNAs as a diagnostic tool for NAFLD. In this study, we found that the posttest fasting blood glucose level decreased significantly after 8 weeks of exercise interventions compared to pretest in the selected HBRE (15.03%) and GBET (16.26%) groups. Furthermore, it was found that there was no significant difference between the two exercise groups.

The results of this study are consistent with the research of Tornese *et al.*,[15] Iraji *et al.*,[30] Khalil Tahmasbi *et al.*,[31] Zaharieva *et al.*,[32] Kim *et al.*,[33] and Haffar *et al.*[34]

Planning an exercise management program for adolescents with T1D involves monitoring blood glucose levels before, during, and after exercise and adjusting appropriate exercise training strategies. Continuous glucose monitoring (CGM) provides accurate information about blood glucose levels and trends before, during, and after exercise. Although there is no target range for blood glucose levels for optimal athletic performance, studies have not demonstrated any difference in athletic performance skills during acute hyperglycemia compared to normal glycemic status. CGM provides more complete information on hyperglycemia correction strategies and hypoglycemia prevention than self-monitoring of blood glucose (SMBG). Advances in technology have made CGM more accessible and user-friendly, allowing for real-time monitoring and alerts.[35]

The findings of this study indicated a significant decrease in glycosylated hemoglobin levels compared to the pretest in the HBRE and GBET groups, with no significant difference between the two groups. The study's findings were consistent with those of previous studies[36] and were not similar to those reported by Banaei *et al.*[37] Regular physical activity based on the recommendations of the International Diabetes Association or the American Sports Medicine Association for 5–6 days a week and 60 minutes per session can have a positive impact on HbA1c levels in diabetic children. Results of a systematic review study indicated that exercise interventions can significantly reduce HbA1c and insulin dose per day and increase cardiorespiratory fitness in children and adolescents with T1DM, and longer interventions and high-intensity GBETs may be more effective in improving these parameters. The findings provide a basis for future studies on how to plan and prescribe exercise programs among diabetic children.[19]

This study found no significant changes in insulin levels between the pretest and posttest in the selected HBRE and GBET groups. Both types of exercises had a role in increasing insulin levels in diabetic adolescents, but HBRE was preferred over GBET. Our findings in this regard were consistent with Chetty *et al.*,[35] Kim *et al.*,[33] and Lu *et al.*,[38] but were not similar to Banaei *et al.*[37]

The insulin signaling cascade leads to several signals and patterns in the plasma membrane, ensuring the use and transfer of GLUT-4. When insulin response is disrupted or stopped completely (e.g. in T1D), the key mediator for glucose transport or GLUT-4 cannot perform its function, leading to metabolic diseases. The precise mechanism by which exercise causes GLUT-4 transport and movement remains unclear, but muscle contraction activates AMP-activated protein kinase (AMPK), indicating that exercise leads to increased exocytosis and decreased endocytosis of GLUT-4.[39]

This study found a slight and non-significant increase in insulin resistance levels in the both HBRE and GBET training groups after 8 weeks of exercise interventions. Previous studies on insulin resistance have reported conflicting results. Recent studies have emphasized that even severe genetic mutations involving insulin receptors lead to increased blood sugar, hyperinsulinemia, ovulatory dysfunction, hyperandrogenism, acanthosis, and excessive soft tissue growth, but no manifestations of insulin dysfunction are observed.

The pathogenesis of insulin resistance is complex and involves multiple factors, such as genetics, lifestyle, and environmental factors. Exercise has been shown to improve insulin resistance by increasing insulin sensitivity and glucose uptake in skeletal muscle. However, the optimal exercise regimen for improving insulin resistance is still unclear.[40-42]

It is suggested that to obtain clearer association between the two exercise protocols and insulin level and insulin resistance, the intervention should be continued for a longer duration, such as 12–24 weeks.

Though many studies reported the relationship between aerobic fitness and many diseases, especially in children,[43,44] physical activity is known to be a major component for controlling obesity and diabetes in children, but which type of exercise is most effective is still debated. Some studies suggest that combined resistance and aerobic exercises may be more effective than resistance or aerobic exercises alone to control lean body mass and body composition. However, training status, exercise intensity, exercise duration, sex differences, and nutrition have all been shown to affect cellular expression responsible for fat oxidation rate. Resistance exercise can increase mitochondrial enzymes and fatty acid transporters, resulting in increased fat oxidation. GBET is also known to increase catecholamines, especially epinephrine, which increases lipolysis, the main factor in releasing fatty acids from adipose tissue.[45] Some studies have shown that GBET can reduce subcutaneous fat, especially in the abdominal area and total body mass.[22,46]

In this study, there were limitations, such as the number of participants and the lack of precise monitoring of the diet and daily activities of the participants.[47] It is suggested that future studies use larger sample sizes and longer exercise interventions. To achieve more clearer conclusion, it is recommended to use exercise interventions with longer durations (e.g. 6 months or more) in future studies due to the minor changes that occur in blood proteins in the short term. To investigate the effects of different training methods from a sustainability perspective, it is suggested to conduct research with various exercise interventions, especially on other miRNAs that are associated with metabolic control of the patients with T1D and have limited research conducted on their effects.

CONCLUSION

The findings of this study found that 8 weeks of selected GBET and HBRE groups led to reduced liver enzyme, improved glycemic control, and a slight increase in hsa-miR-21a. These indices are predictors of the risk of fatty liver and T1D, and better glycemic control as well as liver function can lower the risk of NAFLD and its related comorbidities. Therefore, it can be cautiously concluded that regular physical activity, especially selected GBET and HBRE groups, has positive effects on the main variables of research and can improve the indicators of T1D.

Ethics approval and consent to participate

This study protocol was reviewed and approved by the ethics committee of the University of Isfahan (Code NO: IR.UI.REC.1401.125). Informed consent was submitted by all subjects and parents when they were enrolled. This is a randomized clinical trial registered at the Iranian Registry of Clinical Trial Center (IRCT20200326046861N2).

Conflicts of interest

There are no conflicts of interest.

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