ORIGINAL ARTICLE

Impact of an 8-week home-based resistance training and leisure-time physical activity on serum glucagon-like peptide-1 and microRNA-192 levels in children with type 1 diabetes: A randomized clinical trial

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Background: While numerous studies highlight the significant health benefits of physical activity, there is limited research on the effect of various exercise training in children with type 1 diabetes mellitus (T1DM). The current study aimed to investigate the effects of physical activity on the expression of microRNA (miRNA)-192, serum glucagon-like peptide-1 (GLP-1) level, and some factors related to T1DM in children. **Materials and Methods:** In this randomized clinical trial study, a total of 20 children with T1DM were randomly divided into the following two groups and trained for 8 weeks: home-based resistance training (HBRT) (n = 10, age = 12.6 years) and leisure-time physical activity (n = 10, age = 12.4 years). Metabolic biomarkers, serum levels of miRNA-192, GLP-1, and other relevant measurements were assessed in each patient 48 h before and after completing the 8-week training program. **Results:** The findings showed that in both the training groups, fasting blood glucose concentrations decreased significantly, and maximum oxygen consumption (VO_2 max) increased significantly ($P \leq 0.05$). Furthermore, a significant difference was identified between the cardiovascular endurance (VO_2 max) levels of the two groups, with the HBRT group demonstrating a more substantial improvement. Although increased levels of fasting insulin and decreased levels of glycated hemoglobin were not significant in both the groups ($P \geq 0.05$), a significant increase was observed in the GLP-1 serum levels of both the groups and their miRNA-192 levels decreased by 58%–60% ($P \geq 0.05$). **Conclusion:** Encouraging children with T1DM to do appropriate exercise training workouts at home as well as proper physical activities during their leisure time can be effective in reducing potential complications in patients and improving their health.

Key words: Exercise training, glucagon-like peptide-1, microRNAs, type 1 diabetes mellitus

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INTRODUCTION

The basic characteristic of type 1 diabetes mellitus (T1DM) is chronic hyperglycemia, caused by the destruction of some pancreatic β-cells and the complete loss of insulin.[1] The main causes of T1DM include genetic background, environmental factors, and autoimmune disorders, through which the patient is completely dependent on the external source of insulin to survive and control blood sugar levels.[2] Different studies show that for T1DM, 70% of pancreatic β-cells are destroyed, and the remaining are forced to increase the levels of insulin and overcome its deficiency. It gradually leads to the induction of fatigue and acceleration of apoptosis of β-cells. Therefore, managing the remaining β-cells through controlling metabolic features offers new treatment measures for this disease.[3]

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A wide range of research indicates that some miRNAs (miRNAs) play an important role in diabetes, including miRNA-192.[4,5] In type 1 diabetes (T1D), miR-192 has been found to be dysregulated, leading to impaired β-cell function. Pan *et al*. demonstrated that miR-192 in mice with T1D inhibits insulin secretion by inducing apoptosis in β-cells and inhibiting their proliferation in the pancreas. They also reported that serum level of miR-192 increases in T1DM patients, and there is a positive correlation between miRNA-192 levels, age, and glucose concentration.[6] It has been revealed that the expression of miRNA-192 suddenly increases in prediabetes,[7] and it can be considered a biomarker for predicting diabetic nephropathy among diabetic patients.[8] Furthermore, the upregulation of miR-192 plays a role in reducing the expression of glucagon-like peptide-1 (GLP-1), which subsequently inhibits insulin secretion, ultimately leading to the onset and advancement of T1DM.[6] GLP-1 is a member of the incretin family, specifically a glucagon-like peptide, whose secretion is stimulated by intestinal mucosal cells following the consumption of food.

GLP-1 stimulates insulin release in a glucose-dependent manner, meaning it enhances insulin levels when blood sugar levels are high. This specific peptide is recognized as a valuable anti-diabetic agent that helps regulate blood sugar levels through several mechanisms at the cellular level. These mechanisms involve the promotion of insulin secretion from β-cells, the prevention of excessive glucagon release from pancreatic α-cells, and the reduction of gastric emptying speed, which plays a role in appetite control.[9] Moreover, as clinical trials proved, GLP-1 can reduce the apoptosis of pancreatic β-cells, stimulate their proliferation, and increase their survival.[10] Considering its function, GLP-1 has the potential to be used as an antidiabetic drug, causing insulin secretion, independent of glucose.[11] Understanding the relationship between miR-192 and serum GLP-1 levels is necessary to underlying mechanisms contributing to β-cell dysfunction and managing this disease in children.

The American Diabetes Association recommends regular exercise for all people with diabetes and acknowledges it as a valuable nonpharmacological intervention. In this regard, increasing physical activity can be a remedy to help treat and prevent the complications of the disease.[12] Although some animal studies and studies on type 2 diabetes have provided evidence suggesting that exercise can modulate the expression of miR-192 and enhance GLP-1 secretion,[13] investigations examining the impact of exercise on GLP-1 and miR-192 levels in individuals with T1DM are notably lacking in the academic literature. It is yet to be determined how exercise interventions affect miR-192 and GLP-1 levels in individuals with T1DM. Given the rising incidence of T1D, inadequate glycemic control among patients, and the potential benefits of physical activity in managing T1D and preventing complications, this study aimed to assess the effects of structured resistance training and leisure-based physical activities on glycemic control, anthropometric measurements, GLP-1, and miR-192 levels in children with T1DM.

MATERIALS AND METHODS

Study design

In this study, we performed a randomized clinical trial involving children with T1DM. The initial sample size was established at 24 individuals, informed by prior published research and calculated using G*Power software (version. 3.1.9.7; Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany). To account for potential attrition during the intervention, the sample size was increased by two, resulting in a final selection of 26 participants. However, data from six individuals were excluded due to withdrawal or classification as outliers. After evaluating the normality distribution of the data, the final sample size was adjusted to 20 participants (seven as boys and thirteen as girls). The CONSORT diagram of participants' recruitment is presented in Figure 1.

All participants had received their diagnosis of T1D at least 2 years prior to the study's initiation. In addition, none of the participants had taken part in any regular exercise regimen for the year preceding the study, and according to the health questionnaire, they did not have any illnesses that would impede their ability to engage in exercise training. The patient characteristics are summarized in Table 1. Initially, a nonrandom sampling method was employed to select participants from the available sample pool. Following this,

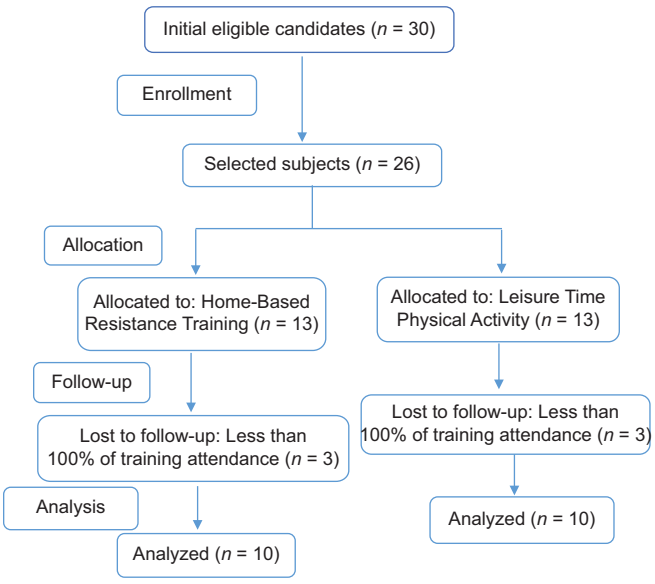

Figure 1: CONSORT flowchart of participants for recruitment, application, follow-up, and analysis

the chosen subjects with using the simple randomization method were assigned to two separate groups:

1. Home-based resistance training (HBRT): Participants performed resistance exercises three times a week and planned as home-based exercises (the individual's body weight was used as the resistance)
2. Leisure-time physical activity (LTPA): Participants were required to participate in their leisure activities, such as football, cycling, volleyball, and other physical activities.

Concerning the HBRT group, the values of intensity, duration, and increases in the exercise load were carefully controlled. To this end, the patients did their exercises under the supervision of the researcher once a week, while they recorded activities for home sessions (twice a week). Videos were sent weekly to the research team. To progressively increase the training load on a biweekly basis, an additional five repetitions were added to the number of each exercise, or the duration of each exercise was extended by 5 s. Figure 2 represents the summary of the exercise program for the HBRT group.

In the LTPA group, subjects participated in leisure-time activities, such as walking, running, cycling, swimming, and ball sports, 3 days a week, with a requirement of a total of 150 min of regular physical activity each week. In this group, the intensity and type of exercises were not controlled, and subjects engaged in physical activities of their choice. According to reports from the LTPA group participants, 3 of the 10 individuals were actively involved in volleyball, 1 in basketball, 3 in soccer, 2 in swimming, and 1 in cycling. The choice of exercise forms in the LTPA group was adapted to the participants' lifestyles and preferences, emphasizing enjoyment and satisfaction from the activity while maintaining continued participation. Participants were asked to schedule their training sessions at least 48 h apart to ensure adequate rest between consecutive sessions. Researchers carried out weekly random observations of the sports classes within the LTPA group to evaluate the level of participant engagement in sporting activities.

Noteworthy, parents completed the general and health information questionnaire and signed the written consent for voluntary participation in the research. This research was conducted after receiving approval from the Research Ethics Committee at the University of Isfahan, identified by the reference number IR.UI.REC.1400.155. Furthermore, it was registered with the clinical trial center of Iran, bearing the registration number IRCT20200326046861N2.

Table 1: Forward/reverse primer sequences

Sequence name	Sequence
Forward primer	5' - GGGGCTGACCTATGAATTG - 3'
Primer reverse	5' - TGTGTTGGCTGACCTATGAATTG - 3'
Primer stem loop	5' - GTTGGCTCTGGTGCAGGGTCCGAGGTA TTCGCACCAGAGCCAACGGCTGT - 3'

Physiological and physical measurements and blood sampling

Physiological measurements, exercise tests, and initial blood sampling were taken 48 h before and after the beginning of the 8-week training program. Blood sampling was done by collecting 3 mL of blood of each patient's brachial vein at the sitting position 12 h after fasting.

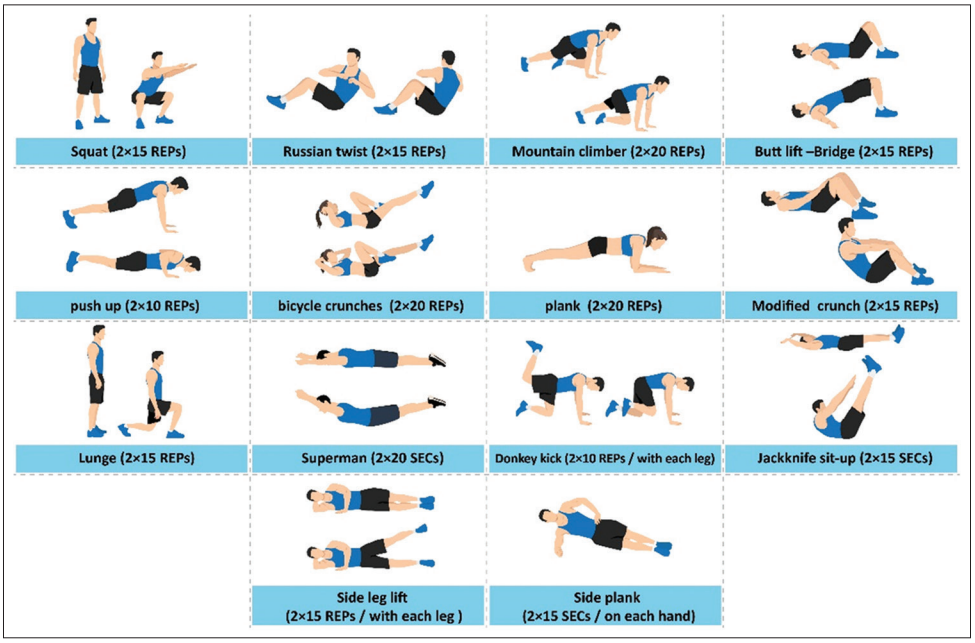

Figure 2: The summary of the training program for the home-based resistance training group

Before and after the study, we conducted a thorough analysis of various health indicators including fasting glucose, insulin, hemoglobin A1C (%), and estimated average glucose (EAG) levels. In addition, we measured body mass index (BMI), skeletal muscle mass, maximum oxygen consumption (VO_2 max), and body fat (%) to gain a comprehensive understanding of the participant's overall health and fitness.

Glucagon-like peptide-1 level assessment

The enzyme-linked immunosorbent assay technique was employed to measure GLP-1 levels. The measurement was carried out using a ZellBio kit (Germany) and according to the manufacturer's instructions.

miR-192 serum levels assessment (reverse transcription-quantitative polymerase chain reaction)

The RT-QPCR method was applied to measure the serum level of miRNA-192. 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. The cDNA synthesis kit was used for reverse transcription (RT) of the extracted RNAs based on the manufacturer's recommended protocols. Then, the human miRNA-192 sequence was extracted from the miRBase database, and the desired primers were designed by the web-based software miRNA design tool to perform RT and quantitative polymerase chain reaction (qPCR). The processes of RT and qPCR were carried out using the kit prepared by the Ansal company (Tehran, Iran), including primer sequences and SYBR Green-based master mix. In this study, U6 was considered a control gene. Table 1 represents the primer sequences. RT was performed according to the technique provided by the kit, and qPCR was performed using Rotor-Gene-6000, Corbett Research (Sydney, Australia) during 40 two-stage cycles including 30 s at 95° and 30 s at 60°. The melting test was carried out at 65°–95° by 1° increments. The findings were analyzed by the Relative Expression Software Tool (REST) software (Technical University Munich, and QIAGEN, Hilden, Germany) to calculate the fold changes, based on the comparative $2^{-\Delta\Delta Ct}$ method. Results were represented based on the Δct of pre- and posttest of each group as well as their fold changes.

Statistical analysis

Descriptive statistics were utilized to calculate the mean and standard deviation for the variables examined in this study. To evaluate the assumptions necessary for conducting an analysis of covariance (ANCOVA), the Shapiro–Wilk test was performed to assess normality, alongside Levene's test to evaluate the homogeneity of variances. In addition, the homogeneity of regression slopes was analyzed. To facilitate comparisons of data both within and between the groups, dependent *t*-tests and ANCOVA were employed, incorporating baseline values of the measured variables as covariates. A significance level of 0.05 was established for all statistical analyses, which were executed using SPSS 23.0 software (IBM Corp., Armonk, NY, USA).

RESULTS

Table 2 shows the mean values of physical and biological health indicators of participants before and after the 8 weeks of controlled exercise and leisure-time activity. Furthermore, Table 2 represents the details of these data statistical analysis. The findings obtained from the covariance test showed a significant difference between the VO_2 max values of the two groups. This feature considerably increased in the participants of both the groups, though VO_2 max in HBRT was greater than that of the LTPA group. The results achieved from the paired *t*-test for intragroup change measurements show that after an 8-week training program, fasting blood glucose concentrations showed a significant decrease among both the groups, with a reduction of 30 and 35 mg/dL in the LTPA and HBRT

Table 2: Descriptive and physiological characteristics of participants before and after the 8-week training and also results related to the statistical analysis of data

Measured variables	Stage	LTPA	HBRT	ANCOVA (*P*)
Age (year)	-	12.4±0.8	12.6±1.3	-
Skeletal muscle mass (kg)	Pre	20±4.7	17.6±3.1	0.452
	Post	20.4±4.8	17.9±3.2	
	t-test (*P*)	0.003*	0.065	
Body fat percentage (%)	Pre	26.6±8.2	24.1±8.7	0.767
	Post	27±8.2	24.4±8.5	
	t-test (*P*)	0.318	0.407	
BMI (kg/m^2)	Pre	22±6.6	18.2±3.6	0.276
	Post	22.4±7	18.2±3.7	
	t-test (*P*)	0.017*	0.576	
Fasting glucose (mg/dL)	Pre	215.80±66.05	244.70±83.57	0.500
	Post	180.70±52.33	214.50±80.37	
	t-test (*P*)	0.027*	0.046*	
Insulin (μIU/mL)	Pre	0.820±0.46	0.79±0.54	0.663
	Post	1.29±1.30	1.09±0.42	
	t-test (*P*)	0.240	0.054	
HbA1c (%)	Pre	9.20±1.28	9.19±2.16	0.542
	Post	9.00±1.32	8.83±1.67	
	t-test (*P*)	0.244	0.200	
EAG (mg/dL)	Pre	217.70±36.86	217.10±61.94	0.561
	Post	211.80±38.11	206.90±47.80	
	t-test (*P*)	0.229	0.204	
VO_2 max (mL/kg/min)	Pre	39.68±3.72	42.26±3.55	0.023*
	Post	40.97±4.54	43.08±3.98	
	t-test (*P*)	0.002*	0.019*	

*Significant values. Data are presented as mean±SD. BMI=Body mass index; EAG=Estimated average glucose; HbA1c=Glycated hemoglobin; HBRT=Home-based resistance training; LTPA=Leisure-time physical activity; ANCOVA=Analysis of covariance

groups, respectively, after 8 weeks. However, the changes of glycosylated hemoglobin (HbA1c), EAG, and body fat percentage were insignificant. Furthermore, insignificant increases were observed in BMI and skeletal muscle mass volume for the LTPA group. Similarly, the insulin levels slightly increased but were not statistically significant.

Glucagon-like peptide-1 levels

The results demonstrated that after an 8-week training regimen, both the groups showed considerable increases in GLP-1 levels. Notably, participants in the HBRT group exhibited a markedly greater increase of 3.7 pg/mL, in contrast to the LTPA group, which recorded an increase of 2.5 pg/mL [Figure 3].

MicroRNA-192 levels

Figure 3 illustrates the comparison of ΔCt values for circulating miRNA-192 prior to and following the 8-week exercise program across both the groups. It is important to note that an increase in ΔCt values indicates a reduction in gene expression. The findings reveal a significant decrease in circulating miRNA-192 levels in both the training groups after the 8-week period, with no notable differences between the groups. In addition, we computed the fold-change values for each group, which indicated that after 8 weeks of training, the participants experienced a reduction in circulating miRNA-192 levels by 58%–60% relative to their baseline measurements.

DISCUSSION

This research sought to assess the impact of an 8-week intervention of organized exercise and LTPA on levels of GLP-1 and miRNA-192, glycemic regulation, and various biological functions in children diagnosed with T1DM. The findings indicated that the 8-week HBRT and LTPA led to a reduction in participants' fasting glucose and EAG levels, while also resulting in a slight increase in their VO_2 max and insulin levels.

Moreover, we found that both the training programs caused a significant decrease in the GLP-1 levels and markedly decreased the circulating miRNA-192 levels in these patients. Despite their critical function in individuals with T1D, there is a lack of research studying the effect of exercise training on GLP-1 and miRNA-192 in this population. GLP-1 is a hormone that plays multiple roles, such as promoting insulin secretion, inhibiting glucagon release, and slowing gastric emptying, all of which help regulate blood glucose levels and improve glycemic control. On the other hand, miRNA-192 is involved in various cellular processes, and it has been shown that its levels are significantly increased in individuals with T1D. More specifically, miR-192 has been shown to suppress the expression of GLP-1, leading to decreased insulin production.

miRNAs play critical roles in regulating diverse physiological processes, including exercise adaptation and disease pathogenesis.[14] Previous studies demonstrated that the values of miRNAs can change as the result of the body's adaptation to exercise activities.[15] Moreover, the level of miRNAs may fluctuate depending on the type of exercise, and it is related to the phenotypic characteristics of exercise, such as VO_2 max. These changes can indicate the effect of the body's immune system responses to exercise or may be due to changes in the fitness of skeletal and cardiac muscles following regular physical activities.[16] In line with these findings, our study identified a significant increase in VO_2max, which may contribute to altered miRNA-192 expression. Until now, no study has documented the impact of exercise training on miRNA-192 levels in people with T1D. Nevertheless, a reduction in the expression of miRNA-192 has been observed in prediabetic individuals following prolonged exercise training. Studies suggest that exercise training, as a therapeutic approach for those with diabetes, can restore miRNA-192 levels to baseline and aid in the normalization of metabolic parameters.[7] However, the specific mechanisms by which exercise training influences changes in miRNA-192 expression remain inadequately understood.

On the other hand, despite the significant decrease in the expression of miRNA-192, we observed a slight increase in

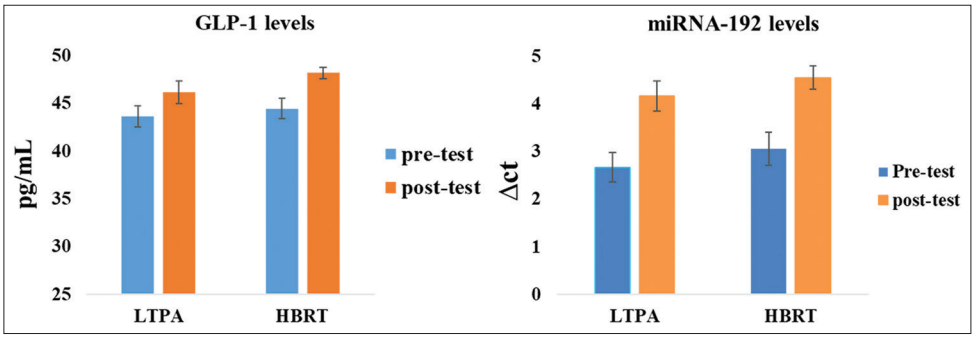

Figure 3: The measured values of glucagon-like peptide-1 and microRNA-192 before and after 8 weeks of training in two experimental groups. HBRT = Home-based resistance training; LTPA = Leisure-time physical activity; GLP-1 = Glucagon-like peptide-1; miRNA-192 = MicroRNA-192

the insulin levels of the patients. Currently, insulin is the best treatment option for T1DM; however, insulin treatment is ineffective to improve the excessive secretion of glucagon in patients with T1DM.[11] GLP-1 can stimulate the secretion of insulin from β-cells and inhibit the secretion of glucagon from α-cells. In contrast, drug interventions using GLP-1 agonists lead to side effects in the digestive system of some patients.[17]

A further beneficial outcome of our research was the elevation of serum GLP-1 levels following exercise training, particularly in the context of resistance exercises. Consistent with our findings, previous research has shown that exercise, regardless of its intensity, affects GLP-1 levels.[18] According to the findings of Lee *et al*., aerobic exercise performed at an intensity between 45% and 80% of the reserve heart rate was associated with increased serum GLP-1 levels and a decrease in both insulin resistance and fasting glucose. Nevertheless, the study indicated that higher intensity exercise produced more favorable results among participants.[19] It has been suggested that GLP-1 plays a role in interacting with the hypothalamus to manage and reduce food intake.[6] In individuals diagnosed with T1D, the reduction in food consumption attributed to GLP-1 may present further benefits. By minimizing food intake, there is a likelihood of decreasing the insulin dosage needed, as the amount of insulin required is frequently based on carbohydrate consumption levels.[17,20] In addition, GLP-1 does not cause insulin secretion at low blood sugar levels, and it can effectively reduce both the HbA1c level and the risk of hypoglycemia.[21]

In addition to the observed beneficial effects of exercise on serum GLP-1 levels and its potential advantages for individuals with T1D, the underlying physiological mechanisms by which exercise enhances GLP-1 secretion further elucidate this relationship. GLP-1 secreted by intestinal L-cells enters the systemic circulation and binds to GLP-1 receptors (GLP-1R) in various tissues to exert its effects. Phosphorylation of AMP-activated protein kinase (AMPK) enhances the binding of GLP-1 to GLP-1R.[22] GLP-1 secretion from L-cells is stimulated by increases in cytosolic Ca^{2+} and cAMP, mediated by receptor and second messenger pathways.[23] Exercise increases the AMP/ATP ratio and AMPK protein levels[24] and alters bile acid profile and short-chain fatty acids (SCFAs), potentially influencing L-cell secretory capacity. Bile acids and SCFAs stimulate GLP-1 secretion through G protein-coupled receptors (GPCRs).[25] These findings suggest that exercise training may increase endogenous GLP-1 concentrations through the GPCR-Ca^{2+}/cAMP axis.[22] However, further research is required to fully elucidate the mechanisms by which exercise stimulates GLP-1 secretion.

Due to the increase in GLP-1 level, our results showed that the fasting glucose level significantly decreased, and HbA1c decreased slightly in both the exercise groups. HbA1c is a reliable gold standard for screening and monitoring diabetic patients.[26] The findings of our study are supported by the results presented by Wróbel *et al*., who reported that there was no significant reduction in HbA1c levels after intervention with aerobic and resistance exercise training in diabetic persons.[27] In general, exercise can improve blood sugar control in diabetes. However, the relationship between different exercise interventions in diabetes control remains unclear.[28]

This is when several research studies concluded that glycemic control can be improved by resistance training alone[29] and suggested that significant reductions in HbA1c by resistance training may be a result of improved storage and utilization of muscles.[26] Some studies show that a combination of aerobic and resistance exercises has a greater effect on blood sugar control compared to these exercises performed separately.[29] This is when several research studies concluded that glycemic control can be improved by resistance training alone[30] and suggested that significant reductions in HbA1c by resistance training may be a result of improved storage and utilization of muscles.[27] In this study, although a significant improvement was observed in some measured variables in diabetic adolescents, it seems that the intensity of exercises is an important factor that was at a low level in this type of exercise. Current guidelines recommend at least 150 min of aerobic activity per week or 75 min of vigorous exercise or strength training 3 times per week.[31] The small sample size, the lack of a control group, and the lack of between-subject dietary control represent important limitations of this study. Therefore, these factors should be considered when interpreting the findings from this study for future research.

CONCLUSION

The present study demonstrated the beneficial effects of two distinct physical activity interventions, HBRT and LTPAs, in patients with T1D. Both interventions were associated with increased GLP-1 levels, reduced circulating miRNA-192 levels, and improved blood glucose regulation, highlighting their potential role in diabetes management. These findings suggest that structured, home-based resistance exercises and self-directed LTPAs may serve as practical, accessible strategies to mitigate metabolic dysregulation and support treatment outcomes in this population. However, further research is needed to explore the effects of different types and intensities of exercise on miRNA-192 levels and overall metabolic health in individuals with T1D.

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Conflicts of interest

There are no conflicts of interest.

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