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Effects of two selected resistance exercises and recreational sport activities on microRNA-148a expression and cardiometabolic risk factors of children with type 1 diabetes

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Abstract

Background: Metabolic diseases such as type 1 diabetes is considered the most important threat factor for cardiovascular complaint. Although the pathological mechanisms underpinning the development of T1D are delicate to define, better understanding of the molecular aspects is most important to identify new remedial targets.

Aim: Evaluating of the effect of two selected resistance and recreational sport activities on microRNA-148a expression and some biomarkers in children with type 1 diabetes.

Materials and Methods: Twenty type 1 diabetic children were assigned randomly to resistance exercise (RE), (n=10, age=12.6 years), and recreational sport activities (RSA), (n=10, age=12.4 years) groups. Participants engaged in an 8-week exercise training, 3 sessions/week. The miR-148-a, HbA1c, glucose, insulin, and HOMA-IR levels have been assessed before and after exercise interventions.

Results: Following the exercise interventions, the concentration of miR-148-a exhibited a non-significant increase in both groups. Nevertheless, no significant differences were noted in the reduction of insulin resistance or in the levels of insulin itself ($P \leq 0.05$). The level of HbA1c decreased but the cardio-respiratory endurance of subjects increased.

Conclusion: Both the resistance and recreational sport activities were effective to improve in cardiorespiratory fitness, diabetic markers, and miR-148a changes that seem to be indicative of the pathological status of type 1 diabetic children.

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1. Introduction

Exercise training is an important component in controlling type 1 diabetes mellitus (T1D) [1]. Engaging in physical activity on a regular basis is linked to a decreased likelihood of developing cardiovascular disease in the future, enhanced maintenance of healthy blood sugar levels over time [2]. Children who have type 1 diabetes are advised to engage in physical activity on a regular basis due to the advantages associated with doing so [1].

The American Diabetes Association recommends that adolescents with type 1 diabetes get 150 min of moderate-intensity activity per week. Despite these guidelines, type 1 diabetics are less active than healthy adolescents, with more than 60% of type 1 diabetics not engaging in physical activity [3, 4].

Several factors contribute to this, including a lack of time, motivation, and support. In addition, the risk of hypoglycemia is another frequently cited obstacle to physical activity. Hypoglycemia can be difficult to predict and symptoms are often masked by exercise or competitive stress [5]. Linked to fear of hypoglycemia another obstacle is the lack of knowledge about effective exercise training programs to prevent hypoglycemia [6].

Typically, the objective of the treatment is to maintain an appropriate level of glucose concentration during exercise training close to physiological normal as possible while avoiding dangerously low or high blood glucose levels [7, 8]. Involving physical activity leads to metabolic enhancements related to insulin sensitivity and glucose uptake [3]. Physical activity also diminishes the likelihood of cardiovascular-related death and is linked to the reduction of factors associated with disease progression, such as chronic hyperglycemia and non-alcoholic fatty liver disease [9, 10].

Certain studies highlight the importance of children with type 1 diabetes participating in a combination of aerobic and resistance exercises for a minimum of three sessions per week, lasting over 12 weeks to achieve effective reductions in their HbA1C levels [11]. The primary challenge when it comes to physical activity is the concern about hypoglycemia. Despite the fact that exercise typically results in decreased blood sugar levels, individuals may need to adapt their insulin dosages and carbohydrate consumption accordingly [12]. Regrettably, these alterations can have unpredictable outcomes and may result in dysglycemia [11].

Micro ribonucleic acids (RNAs) are a large subset of non-coding RNAs with between 18 to 25 nucleotides [13]. These molecules control gene expression after transcription by inhibiting translation or induction of decomposition [14]. Since the serum miRNAs concentrations are relatively constant, they can be used as biological markers to diagnose certain diseases [13, 15]. It has been revealed that some circulating miRNAs are linked to several metabolic diseases including, obesity, T1DM [16] and hyperlipidemia [17, 18]. The function of miR-486, miR-148-a, and miR-15b in predicting T1DM has been shown in type 1 diabetic children due to the association of such miRNAs with insulin secretion from the pancreas and glucose intolerance [17, 18].

Furthermore, the miR-148a acts as a new regulator for the proliferation and differentiation of human visceral adipose tissue by targeting the KLF7 gene; meanwhile, fat cells also respond to pre-inflammatory cytokines by a significant enhancement in the expression of miR-148-

a [19, 20]. The miR-148-a is involved in the inflammation of adipose tissue, and may be an essential mediator in the progression of obesity through its transcription mechanism [21].

Available evidence suggests that the circulating levels of some miRNAs related to metabolic disorders such as type 1 diabetes are changed after exercise interventions [22]. The purpose of this study was to examine the impact of two methods of recreational sport activities (RSA) and a resistance training on miR-148-a level, lipid profile, body fat percentage, and VO_2peak of adolescents with type 1 diabetes. We speculate that changes in some circulating miRNAs levels, such as miR-148-a due to exercise interventions in adolescents, may serve as biomarkers to predict the future risk of some non-communicable diseases in adulthood.

2. Materials and Methods

2.1. Participation

Twenty children with T1D aged 10-15 years old were randomly assigned to one of two groups (RE: n= 10, age= 12.6±1.3 years, male= 4; female= 6) and (RSA: n= 10, age= 12.4±0.8 years, male= 3; Female= 7). Main characteristics of all participants are described in Table 1. To make sure that the effects of the exercise interventions were less affected by other covariate variables, participants and their parents were instructed to maintain their regular diet and daily physical activity during the exercise interventions.

The inclusion criteria were as follows: Ages from 10 to 15 years, diagnosis of type 1 diabetes mellitus (T1D) at least one year prior to study commencement, no history of cardiovascular disease; habitually inactive (≤30 min/day, ≤2 days/week). The criteria for exclusion included having current physical injuries or any pre-existing metabolic disorders other than T1D. Withdrawal from participation by the individual for any reason, illness, or injury that prevented them from exercising during the research period, and missing more than three training sessions during the intervention period. All subjects completed the recommended exercise training program, with an average attendance rate of 95% for all sessions. However, two participants from every group were excluded from the final analysis because they were not eligible to participate in follow-up measurements.

Table 1. Characteristics of the participants in the two studied groups at baseline and after the training period

Measured Variables	Groups	Pre-test	Post-test	P-value (pre-post)	P-value (between groups)
Height (cm)	RE (n=10)	157.4 ±8.9	157.9 ±8.9	0.006	0.879
	RSA (n=10)	157.3 ±10.5	157.9 ±10.5	0.006	
Weight (kg)	RE (n=10)	45.3 ±11.9	45.8 ±12.49	0.164	0.028£
	RSA (n=10)	51.9 ±13.2	51.0 ±12.8	0.050	
BMI (kg/m^2)	RE (n=10)	18.2 ±3.6	18.3 ±3.7*	0.509	0.589
	RSA (n=10)	21.9 ±6.6	22.3 ±6.9*	0.01	
BF (%)	RE (n=10)	24.1 ±8.7	24.4 ±8.5	0.001	0.779
	RSA (n=10)	26.7 ±8.2	27.0 ±8.2	0.001	
CRE ($ml/kg^{-1}.min^{-1}$)	RE (n=10)	42.3 ±3.6	43.3 ±3.8*	0.01	0.063
	RSA (n=10)	39.7 ±3.7	41.2 ±4.2*	0.01	

Mean ±SD (P <0.05)
*Differences between time points within the conditions (pre-post); £: Differences between experimental groups; CRE: Cardio-respiratory Endurance; $ml/kg^{-1}.min^{-1}$: Milliliters per minute per kilogram of body mass; RE: Resistance exercise; RSA: Recreational sport activities; BMI: Body mass index; BF: Body fat percentage.

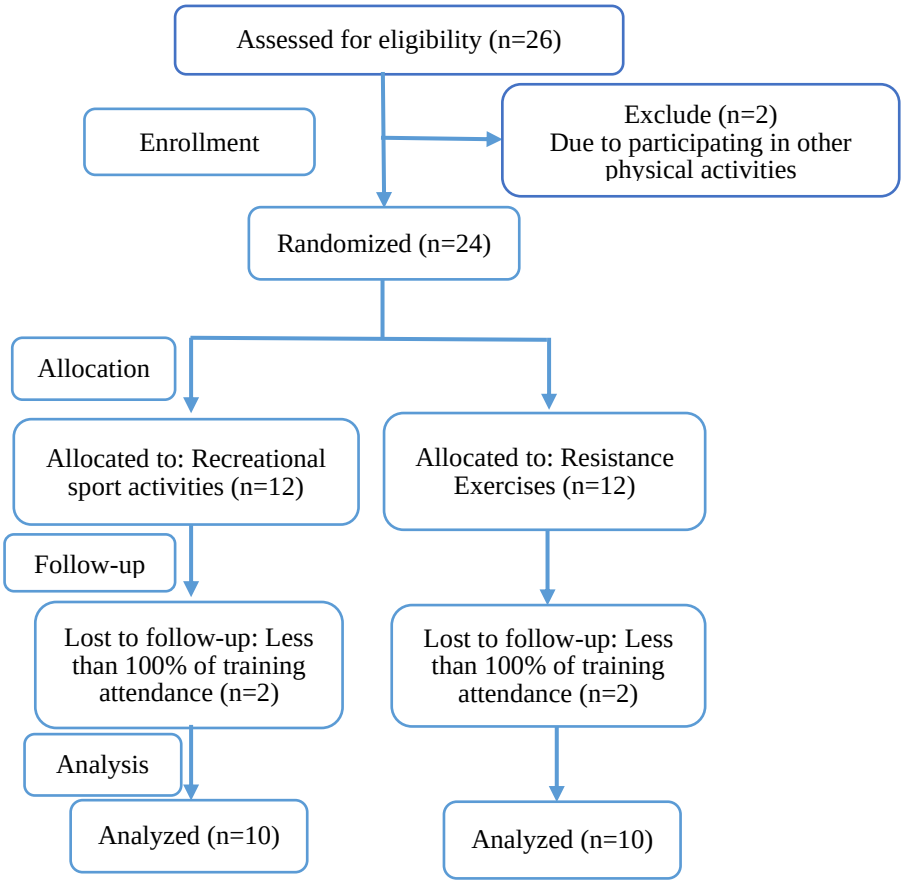


Figure 1. CONSORT flow chart of participants for recruitment, application, follow-up, and analysis

The CONSORT diagram of participants' recruitment is presented in Figure 1. The consent form was obtained from parents, and students before the start of the course.

2.2. Instrument

Anthropometric assessments of weight and height were conducted with precision, recorded to the nearest 0.1 kg and 0.5 cm, respectively, utilizing a calibrated stadiometer (Seca, Germany). The body mass index (BMI) was calculated via dividing the body mass by the square of the height in meters. Body fat percentage (BF %) was determined using a body composition analyzer (InBody-270, Korea). The assessment of cardiorespiratory endurance was conducted through the 20 m multistage shuttle run test, following established protocols. By applying the formula suggested by Matsuzaka et al. (2004) in conjunction with the total number of laps completed by the participants, we calculated the peak oxygen consumption (VO_2peak) [23].

2.3. Biochemical measurements

Samples of blood, amounting to 5cc, were obtained from the left brachial vein of the participants in both the pre- and post-test phases after a 12-hour of overnight fasting (24 hours before and 48 hours after the last training session). The participants were positioned in their seats during the blood collection, and the samples were subsequently placed into test tubes for analysis. The blood samples were then centrifuged at 4°C, with a speed of 3000 RPM, for 10 min, and the resulting serums

were stored at -80°C until they could be further analyzed.

Metabolic biomarkers such as fasting glucose, insulin, insulin resistance, and HbA1c levels were measured by valid methods using kits with Hitachi 917/modular system made by Japan. An automated clinical chemistry analyzer (Roche Cobas®8000) was utilized to conduct biochemical tests on serum for metabolic biomarkers, including fasting glucose, insulin, and HbA1c levels. Furthermore, a valid formula was employed to determine the homeostasis model of assessment of insulin resistance HOMA-IR) [24].

2.3.1. miR148-a serum levels assessment (RT-QPCR)

The RT-QPCR method was used to measure the serum level of miRNA-148a. For this purpose, microRNAs were first extracted from serum samples with the PAXgene Blood miRNA kit (Qiagen, Germany) using the method provided by the manufacturer. A cDNA synthesis kit was used for reverse transcription (RT) of the extracted RNAs according to the manufacturer's recommended protocols. The human miRNA148 sequence was then extracted from the miRbase database and the desired primer was designed using the online miRNA design tool to perform reverse transcription (RT) and quantitative PCR (qPCR). Reverse transcription and qPCR processes were performed using a kit made by Anasal Company (Tehran, Iran) containing primer sequences and SYBR Green-based Master Mix. U6 was considered as a control gene in this study. Reverse transcription was performed according to the technique in the kit and QPCR was performed using a Rotorgen 6000 (Corbette, Australia) for 40 biphasic cycles including 30 sec at 95°, and 30 sec at 60°. The melting test was performed between 65 and 95° in 1° increments. Results were analyzed using REST software to calculate fold changes based on the comparative $2^{-\Delta\Delta Ct}$ method. Results were presented based on pre-and post-test Δct and their refractive changes for each group [25].

2.4. Procedure

The exercise programs were formulated in accordance with the American College of Sports Medicine's guidelines for achieving the most effective exercise intensity, frequency, duration, and type of exercise training for children with diabetes. After conducting investigations, it was discovered that diabetic children tend to be sedentary, but some engage in physical activities at home during the post-COVID period while adhering to their medical conditions. Resistance exercises were performed three times a week and were designed as home-based resistance exercise (RE), so the resistance was human body weight (Table 2). Values for intensity, duration and effort gains in the RE group were closely monitored. 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. In the recreational sport activities (RSA) group, subjects were required to participate in their leisure activities, such as soccer, cycling, volleyball, swimming and gymnastics, three days a week, for a total of 150-210 min of regular exercise per week. Practicing basic sport skills and playing games starting with 50 min/session in the first week, increasing by 5 min every two weeks and about 70 min/session in the final training. Each session included 15 min of warm-up and cool-down exercises.

Table 2. Mean ± SD of biochemical measurements in the two studied groups (RE and RSA) at baseline and after the training period

Variables	Groups	Pre-test	Post-test	Δ (%)	CI 95% for the difference	P-value	
						Time	Group
miR-148-a (ΔCt)	RE	9.34±1.29	10.04±0.89*	7.5	[9.72; 10.52]	0.041	0.272
	RSA	9.57±1.13	9.89±1.14*	3.3	[9.42; 10.21]	0.011	
HbA1c (%)	RE	9.19±2.2	8.23±1.9*	-10.4	[7. 89; 8.57]	0.010	0.133
	RSA	9.2±1.3	8.16±1.4*	-6.5	[8. 25; 8.93]	0.007	
Insulin (µU)	RE	1.098±0.4	0.795±0.5	38.1	[0.495; 1.72]	0.240	0.663
	RSA	1.298±1.3	0.820±0.5	58.3	[0.677; 1.90]	0.009	
HOMA-IR	RE	0.584±0.3	0.524±0.5	11. 5	[0.341; 0.769]	0.566	0.985
	RSA	0.522±0.4	0.417±0.3	25.2	[0.339; 0.766]	0.402	
Glucose (mg/dl)	RE	244.7±83.6	207.9±78.8*	-15.0	[173.7; 219.9]	0.006	0.755
	RSA	215.8±66.1	180.7±52.3*	-16.3	[168.7; 214.9]	0.027	

Mean ± SD; $P<0.05$

*Differences between pre-posttests; Δ(%): Percentage of change between initial and final measurement; RE: Resistance exercise; RSA: Recreational sport activities; HbA1c: Glycated hemoglobin; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance; ΔCt: the difference of expression between 2 genes; mg/dl: Milligrams per deciliter; CI: Confidence interval.

2.5. Statistic

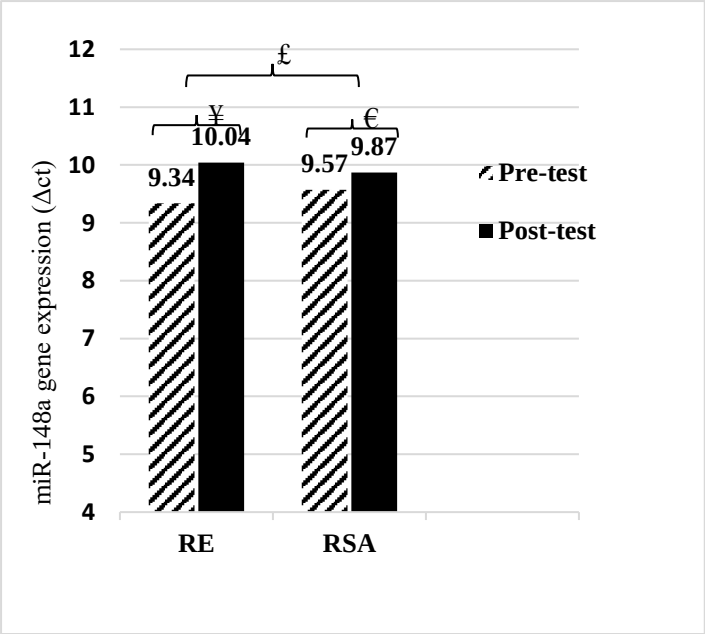
The mean and standard deviation values for the variables were computed using descriptive statistics. The Shapiro-Wilk test was utilized to assess the normality of the data. To assess the impact of the intervention, an analysis of covariance (ANCOVA) was performed, with miR-148-a, metabolic markers, body fat percentage, and VO_2peak changes serving as dependent variables and the baseline values of the measured variables serving as covariates. The data were analyzed using IBM SPSS software version 22 (IBM, Armonk, New York, USA), and a significance level of $P\leq 0.05$ was established.

3. Results

Figure 1 shows a CONSORT diagram providing specific information about the involvement of the 26 individuals who took part in the study. Of these, 24 eligible children with T1D were randomly assigned to two exercise groups, with an equal number in each group. All subjects completed the recommended exercise training program, with an average attendance rate of 95% for all sessions. However, two participants from every group were excluded from the final analysis because they were not eligible to participate in follow-up measurements.

Tables 1 and 2 present the baseline demographic and clinical characteristics of the participants, and no differences were found between the groups in terms of body composition, physical fitness variables, and blood biochemical parameters. This trial initially involved some 26 type 1 diabetic children, but only 20 completed the study with 10 participants in each group. Table 1 displays the characteristics of the participants in the resistance and recreational sport activities groups. At baseline (pre-test), the participants in both groups were similar in weight, BMI, body fat, and VO_2peak ($P>0.05$). Table 2 presents the characteristics and biochemical variables of the participants at baseline and post-test, with no significant differences observed between two groups in all measured variables at baseline. Data analysis showed that the miR-148-a level increased non-significantly for both exercise intervention groups (7.5% in resistance and 3.3% in recreational sport activities; $P=0.272$), insulin resistance decreased (11.5% in resistance and 25.2%

in recreational sport activities; *P*=0.985), insulin decreased (38.1% in resistance and 58.3% in recreational sport activities; *P*=0.663), and HbA1c exhibited certain reductions (-10.44% in resistance and -6.52% in recreational sport activities; *P*=0.133). The cardio-respiratory endurance of the subjects increased (2.53% in resistance and 3.75% in recreational sport activities; *P*=0.063). However, there was a slight increase in the body fat percentage of the participants (1.2% in resistance and 1.46% in recreational sport activities; *P*=0.779), but no significant differences observed between the groups. Figure 2 illustrates that the miR-148-a level changed significantly in both intervention groups at two time points, but there were no significant differences between the two experimental groups.



RE=Resistance exercise, RSA= Recreational sport activities; £= Difference between experimental groups (*P*=0.272). ¥= Difference between pre-post in SRE group; €= Difference between pre-post values in RSA group

Figure 2. Comparison of miR-148a changes in different groups

Table 3. Summary of the selected resistance training at home

Number	Exercises	The number of repetitions/Time	Number of sets	Rest time after each set
1	Standing half squat	15 REPs	2	40 SECs
2	Russian twist	15 REPs	2	40 SECs
3	Mountain climber	20 REPs	2	40 SECs
4	Butt lift –Bridge	15 REPs	2	40 SECs
5	push up	10 REPs	2	40 SECs
6	bicycle crunches	20 REPs	2	40 SECs
7	Plank	20 REPs	2	40 SECs
8	Sicilian crunch	15 REPs	2	40 SECs
9	Lunge	15 REPs	2	40 SECs
10	Breaststroke straighten back	20 SECs	2	40 SECs
11	Donkey kick left	10 REPs (with each leg)	2	40 SECs
12	Crunch toe touch	15 SECs	2	40 SECs
13	Side leg lift right	15 REPs	2	40 SECs
14	Side leg lift left	15 REPs	2	40 SECs
15	Side plank	15 SECs (on each hand)	2	40 SECs

Abbreviations : REPs: Repetitions, SECs: seconds

4. Discussion

In this study, we show for the first time that both selected resistance training and recreational sport activities increased the level of miR-148-a expression (7.5 vs. 3.3%) respectively. An increasing amount of evidence suggests that numerous miRNAs are involved in a diverse range of biological processes, such as cell fate determination, proliferation, cell death, and energy metabolism, by regulating the expression of their targets through both down-regulation and up-regulation; therefore, such findings could be important for health and exercise professionals [21]. Typically, the mir-148a gene is active in different parts of the human body such as the brain, heart, liver, thymus, pancreas, kidneys, placenta, and the hematopoietic system [26]. It is believed that this gene plays a role in regulating gene expression to keep gastric tissue stable, and if it is overexpressed or expressed abnormally, it could lead to the development of gastric tumors [27, 28].

Nielsen et al. (2014) observed the expression of mir-148a and found that exercise could impact its expression levels in the bloodstream. After engaging in continuous exercise for a period of 12 weeks, the expression level of mir-148a in blood circulation considerably decreased [29].

Shi et al. (2015) conducted a study to examine the effects of miR-148a loss on adipogenesis. Their findings showed that the expression of miR-148a was reduced by approximately 60% at day 0 compared to the control. Additionally, the knockdown of miR-148a significantly inhibited adipogenesis, which was indicated by a decrease in the expression of adipocyte-specific factors [21].

The presence of miR-148a-3p was observed in all stages of T1D, indicating that it could serve as a potential early biomarker that is specific to the development of T1D [26, 30]. The molecular mechanisms involved in the chronic adaptation of pancreatic β-cells to hyperglycemia are not fully elucidated. Different experimental models were used to investigate the role of different miRNAs in the control of intracellular pathways critical to insulin signaling. Furthermore, there have been reports of a significant increase in serum miR-148-a levels for regulating fat metabolism genes after a period of exercise with diet [16]. Other studies showed that there was a significant decrease in miR-148 levels after acute and chronic aerobic exercise in diabetic children [6, 31].

Numerous miRNAs that are specific to particular body tissues are expressed during and after exercising, and they stimulate a sensory-motor response to physiological stimuli [16]. The expression profiles of the majority of microRNAs appear to be dependent on the type and intensity of the exercise performed [32], and other training variables such as training mode, training load, and individual differences are effective on training adaptations. It is obvious that the changes in miR-148-a are influenced by various variables and more clinical studies are needed [33]. Further possible mechanisms include exercise-induced stress, oxidative stress, as well as hormonal, mechanical, and osmotic stress, which may eliminate the factors present in the blood and lead to the destruction of miRNAs by RNases. It is, thus, likely to speed up the destruction of the miR-148-a with exercise training [34].

The role of miR-148-a in predicting the risk of T2DM in obese children has been confirmed by the association of such miRNAs with insulin secretion from the

pancreas and glucose intolerance [35]. The inadequate response of miR-148-a to pre-inflammatory cytokines can also be an important mediator in the course of obesity complications [26]. On the other hand, since changes in the intensity of physical activity cause certain adaptations to pre-genetic factors such as miRNA, it is expected that the training methods used will also cause different changes in the expression of miRNAs [16].

The results of this study showed that both exercise interventions had identical effects on the fasting glucose, insulin, HbA1c, HOMA-IR, cardiorespiratory fitness, and body fat percentage of participants. These findings are in line with previous research that has shown that exercise training programs can lead to improvements in metabolic biomarkers related to diabetes and cardiorespiratory fitness. However, it was also observed that children experienced a slight increase in body fat percentage following exercise training [1, 36, 37]. Since, the participants in this study did not have a specific diet, it is likely that due to fear of hypoglycemia, the energy intake of participants increased during exercise interventions. Therefore, the body fat percentage of participants increased slightly.

This study had some limitations that need to be considered. First, a larger sample size would have been desirable. Secondly, we could not control the participants' diet during exercise interventions, affecting the results. Although the participants and their parents were instructed to maintain their eating patterns and physical activity, the changes in measured variables cannot be explained only by the exercise interventions. Furthermore, treatment adherence is a key factor determining training outcomes, and future research should evaluate the responses to recreational sport activities exercise training compared with other modalities. However, this is one of the few studies that examine the effects of selected resistance training and recreational sport activities protocols on the miR-148-a levels of children with T1D. Therefore, further research is needed to achieve overall results.

5. Conclusions

The current study suggests that both resistance training and recreational sport activity methods can be used to regulate metabolic markers of T1D in children, and miR-148-a levels that indicate the pathological status of diabetes in diabetic children. It appears that the types of exercise training interventions, especially recreational sport activities, can be used optimally, because it is more possible to perform this type of exercise and adolescents can do such physical activities with more motivation.

Conflict of interest

The authors declared no conflicts of interest.

Authors' contributions

All authors contributed to the original idea, study design. VM and MKY have made substantial contributions to conception and design, analysis and interpretation of data; SH and MN have been involved in drafting the manuscript and revising it critically for important intellectual content; All authors read and approved the final manuscript.

Ethical considerations

The authors have completely considered ethical issues, including informed consent, plagiarism, data fabrication, misconduct, and/or falsification, double publication

and/or redundancy, submission, etc. Informed consent was obtained from parents of all subjects involved in the study. The study was conducted in accordance with the declaration of Helsinki, and approved by ethics committee of University of Isfahan (no. IR.UI.REC.1401.125).

Data availability

The dataset generated and analyzed during the current study is available from the corresponding author on reasonable request.

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