Original Article

Effects of Two Different School-Based Training on Serum miR15b Expression and Lipid Profile of Adolescents with Obesity

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Abstract

Background: Some circulating microRNAs, such as miR15b, are predictors of diseases associated with adulthood obesity. This study aimed to evaluate the effect of two selected school-based and high-intensity interval training (HIT) on miR15b expression and lipid profile of obese adolescents. **Methods:** Thirty-eight adolescent males (12 ± 1 years) with obesity (body mass: 74.7 ± 13.2 kg, body mass index (BMI): 26.0 ± 2.3 kg/m^2, and body fat (BF): 27.2 ± 3.6%) were randomly assigned to the following based on the age-related body mass index: (i) HIT (n = 13), (ii) school-based exercises (SBE, n = 13), and (iii) control (n = 12) groups. Mir15b was extracted using the RT-PCR system, and lipid profile was studied using the enzymatic colorimetric method before and after 12 weeks. Three training sessions were held each week during the course. **Results:** Following the exercise interventions, in both training groups, miR15b (HIT: –63.8 vs. SBE: –56. 7%; P = 0.001), cholesterol (HIT: –8.8 vs. SBE: –9.2%; P = 0.025), and low-density lipoproteins levels (SBE: –13.1 vs. –20.8%; P = 0.48) decreased; however, the peak oxygen uptake of subjects increased (HIT: 4.0 vs. SBE: 4.0%; P = 0.003). However, there were no significant differences in triglyceride (HIT: –16.9 vs. SBE: –8.3%; P = 0.134), and high-density lipoprotein (HIT: 3.1 vs. SBE: 4.8%; P = 0.479) levels between both intervention and control groups (P > 0.05). **Conclusions:** The results showed that both types of exercises had almost similar effects on reducing miR15b expression and improving the lipid profile. Hence, based on the difficult nature of HIT for children with obesity, further use of school-based exercises is suggested.

Keywords: *Adolescent, circulating microRNA, exercise, obesity*

Introduction

One of the most critical problems worldwide is the prevalence of obesity and its associated consequences.[1] Individuals with obesity are often at risk of various sicknesses such as cardiovascular diseases and diabetes.[2] Nowadays, the prevalence of obesity and its related diseases has increased dramatically in children, leading to some physical and mental impairments and even reducing students' learning capacity.[3] Studies have suggested the positive role of different physical activity patterns in lowering blood lipids, preventing obesity and type 2 diabetes (T2DM).[4,5] The effects of physical activity in this area have been studied and recently focused on school-based exercises (SBE), especially with the participation of parents to improve children's weight and inactivity,[6,7] as such activities are effective in increasing bone mineral density of adolescents and have also been effective in obese adolescents.[6,8]

Micro ribonucleic acids (microRNAs) are short, single-stranded, non-coding RNAs that generally include 20 to 22 nucleotides. Circulating microRNA concentrations are relatively stable and can be used as biomarkers for the diagnosis of some diseases.[9] Reviews have identified that serum microRNAs are associated with numerous metabolic diseases such as T2DM, and hyperlipidemia.[9] Given the available data in this field, it is suggested that there are some associations between some microRNAs such as miR15b, miR138, and miR376a and hepatic insulin resistance in obesity.[1,10] In addition, it seems that they could be used as potential predictive biomarkers for obesity and its related metabolic disorders.[11] Studies have shown that other microRNAs such as miR486, miR146b, and miR15b could predict the risk of T2DM in overweight/obese adolescents,[12] and have essential roles to

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increase obesity and related diseases through their effects on the pancreas, liver, and muscle functions as well as adipose tissue.[13] Additionally, the overexpression of miR15b has been shown to suppress insulin receptor protein expression, and obesity-induced miR-15b is associated with insulin resistance, leading to T2DM.[10] Therefore, the regulatory mechanism of miR15b in adolescents with obesity may be involved in the future development of T2DM as well as fatty liver diseases.[14,15]

The role of different types of exercise training with different intensities on the adaptation process of gene expression is well-established and demonstrates that each exercise training leads to activation of specific signaling pathways.[16] Therefore, a subset of genes regulated by microRNAs may undergo alterations following different exercise training.[17] Yang *et al*.[10] reported a decrease in miR15b expression after 6 weeks of aerobic exercise. Similarly, Xi *et al*. reported that following a period of exercise and diet interventions, serum miR146b levels reduced,[9] whereas Shen Wang *et al*.[18] indicated that exercise in individuals with obesity increased the levels of miR214 and miR126, which are associated with improved endothelial function in obese individuals. Although evidence suggesting that moderate continuous aerobic physical activity and high-intensity interval training (HIT) could positively affect the health of adolescents with obesity, there is a lack of evidence of various modes of exercise and specifically school-based interventions on microRNAs in adolescents with obesity. The main hypothesis of this research is that there could be significant differences between the effectiveness of two different training methods on miR15b expression and the lipid profile of adolescents with obesity. Therefore, the aim of this study was to examine the potential effects of two selected SBE and HIT exercises on miR15b expression and the lipid profile of adolescents with obesity. We hypothesized that HIT and SBE training with identical loads and intensities could have the same effects on miR15b expression and lipid profile in adolescents with overweight/obesity.

Methods

Participants and ethics

Thirty-eight adolescent boys from the schools of Shahrekord were enrolled in this study and randomly divided into three groups based on their age-related body mass index (BMI): (i) HIT (n = 13), (ii) SBE (n = 13), and (iii) control (CG, n = 12) [Table 1]. Inclusion criteria were as follows: boys 11 to 13 years of age; BMI values belonging to a group of overweight or obese boys based on the standards of the Centers for Disease Control (CDC);[4] none of the participants were taking any medication as assessed by a medical health history questionnaire; no history of cardiovascular disease; no additional exercise training; and no new diet during exercise interventions. Exclusion criteria were injury or voluntary withdrawal of participants for any reason, illness or inability to exercise during the research period, and absence of more than three sessions. The written informed consent form was completed by the parents of the selected participants before the study.

This study was registered at the Iranian Registry of Clinical Trials (IRCT20200515047455N1), approved by the University of Isfahan ethics committee (IR.UI.REC.1399.054), and carried out according to the Declaration of Helsinki.

Study design

This study was designed as a randomized controlled trial to compare the effectiveness of selected HIT versus SBE programs on miR15b expression, peak oxygen uptake, and lipid profile of adolescents with overweight/obesity. Participants were matched randomly based on their BMI for either HIT, SBE, or CG groups. To calculate the sample size, we used the G-Power 3.1 software program, and a minimum total sample size of 42 was determined based on the effect size, power, and alpha level, which were set as 0.5, 0.8, and 0.05, respectively.[19,20] According to previous studies and anticipating a 5% dropout rate in subjects during the interventions, the number of subjects increased to 15 in each group. In total, seven subjects dropped out of the study during the exercise interventions, two from the SBE group, two from the HIT group, and three from CG.

Experimental approach

Before the beginning of the study, all participants were familiarized with testing procedures, and measurements of research variables were accomplished. The following outcomes were assessed: (1) anthropometric and body composition (e.g., body mass, height, BMI, and BF); (2) miR15b levels; (3) triglycerides, cholesterol, high-density lipoprotein, low-density lipoprotein; and (4) cardiorespiratory fitness (VO_{2peak}). All measurements were performed at the same time and temperature conditions in a gym as the recommendations given for standard evaluations.

Anthropometric measurements

The height and weight of participants were measured to the nearest 0.5 cm and 0.1 kg respectively, using a digital scale, and a stadiometer (Harpenden, UK Ltd.) based on the published valid guidelines.[21] The BMI was calculated using the following formula: weight/height^2 (kg/m^2). The skinfold thickness of each participant was measured twice by a caliper (Lafayette, model 01127, USA) at four sites (subscapular, triceps, thigh, and suprailiac), and the body fat percentage (BF%) was estimated according to the equation of Peterson *et al*.[22]

Peak oxygen uptake measurements

The participants performed the 20-m shuttle run test on the sports ground of the school. Next, VO_{2peak} was calculated

with 80% validity using Matsuzaka *et al*.'s[23] equation, which is mentioned below.

VO_{2peak} (mL/kg/min) = (61.1–2.20 × gender (0 = male))–(0.462 × age)–(0.862 × BMI)+(0.192 × number of laps).

Blood sampling and analysis

The baseline blood sample was obtained 24 h before the first training session following 12 h overnight fasting, whereas the participants rested in a sitting position and after the 12-week exercise intervention. Samples were centrifuged and frozen at –80°C until analysis. Total cholesterol, HDL cholesterol (HDL-C), and triglyceride levels were assessed by the enzymatic colorimetric method on the 917/modular *P* system (Hitachi, Japan) using Pars Azmoun Iran, manufacturing kit with lot number 97001-3. LDL cholesterol (LDL-C) was calculated using the Friedewald formula.[24]

Measurement of miR15b

Quantitative analysis of miR-15b levels was performed by enzyme-linked immunosorbent assay (ELISA) method, using the biotech kit from Irizol Biotech according to the manufacturer's instructions (RNA Extraction Kit Manufactured by Rena Biotech Co.; access code: RB1001). First, 500 µL of blood was thoroughly mixed with 1 mL of buffer to give a homogeneous solution, which was transferred to a 2 mL microtube. The resulting mixture solution was kept at an ambient temperature for 5 min; then, 200 mL of chloroform was added to the mixture and shaken up and down sharply for 10 to 15 s, and rereleased for 5 min. The tube containing the mixture was centrifuged at 8,000 rpm for 5 min. The light layer containing the RNA-containing supernatant separated and transferred to another tube. Next, 1000 µL of 100% cold ethanol was added to it and then was placed at –20°C freezer for 8 min. Finally, the tube was removed from the freezer and centrifuged as before, and the liquid inside the tube was discarded after centrifuging. To eliminate the DNA from the extracted RNA product, after verifying the RNA quality on 1% agarose gel, 0.5 mL of DNaseI was added to a tube containing RNA at a concentration of 2 ng/mL to a concentration of 500 ng to 5 µg. Then, it was incubated at 37°C for 10 min. The extraction of miR15b was done using a real-time reverse transcriptase-polymerase chain reaction (RT-PCR) system (ABI Step one, USA), and values were calculated (ΔCt). The microRNA database (miRBase) was used to determine the miR15b sequence (5′-uagcagcacaucaugguuu aca-3′).[25]

Exercise intervention

The exercise intervention groups completed three 90-min sessions each week for 12 weeks. High-intensity intermittent training (HIT) and school-based exercise (SBE) have been implemented at their schools or a gym after school hours. Briefly, the HIT program consisted of two to four sets of high-intensity interval running with 85 to 100% maximal aerobic speed (MAS), separated by 5 min of active recovery. Example: (2×[5 × 30 s/30 s] 85% MAS, rest = 5 min) means that the participants had to run two sets of five repetitions of 30 s/30 s, composed of the 30 s running at 85% of MAS and 30 s active recovery at 50% of MAS. Interval distances were individually adjusted according to each participant's MAS determined by the 20-m shuttle run test. Each training session lasted approximately 20 to 45 min, including 15-min warm-up followed by the HIT program and ending with 15-min cool-down exercises.[26,27]

The SBE program was similar to the physical education classes' activity (each session: 60–90 min, 3 days/week) at their local school or a gym after the school hour. Each training session included a 10-min warm-up, 5-min cool down (at the end), and a combination of aerobic and resistance exercises. Aerobic activities include performing the 20 m shuttle run test as a progressive aerobic training (10–15 min) and futsal basic skills practice and playing futsal for 30 to 35 min each session. The time of aerobic exercises gradually increased up to 20 min by weeks 4 through 12. In addition to the aerobic exercises, participants performed some resistance exercises (e.g., sit-up exercises, three sets with a time of 30 s; 10 s was added to the set time every 3 weeks, and in the last week, the time of each set reached 60 s.[4,6] The control group continued their daily activities without any exercise.

Statistical procedure

Descriptive data are presented as mean ± standard deviation (SD) in all analyses. The normality of row data was checked by the Shapiro–Wilk test. The analysis of covariance, paired-*t* statistic, and Bonferroni post hoc test were used to compare the between- and within-group changes in the measured variables. SPSS software version 22 (IBM, New York, USA) was used. The *P* value of ≤0.05 was considered statistically significant.

Results

Thirty-eight adolescent boys aged 12 ± 1 years with a BMI higher than the 95th percentile, and body mass of (i): HIT, 74.0 ± 13.9 kg; (ii) SBE, 75.1 ± 12.0 kg; and (iii) control, 75.1 ± 14.9 kg engaged in this study. There were no significant pre-training differences between HIT, SBE, and CG groups for body weight, BMI, BF, and peak oxygen uptake (VO_2 peak) of groups ($P > 0.05$) [Table 1]. The results of ANCOVA with adjustments for baseline values as covariate variables showed improvements in the mean levels of miR15b (HIT: 3.41 vs. CG: 7.91, $P = 0.001$; SBE: 3.61 vs. CG: 7.91, $P = 0.002$; HIT: 3.41 vs. SBE: 3.61 ΔCt, $P = 1.00$), cholesterol (HIT: 146.0 vs. CG: 153.20, $P = 0.084$; SBE: 137.8 vs. CG: 153.20, $P = 0.037$; HIT: 146.00, vs. SBE: 137.8, mg/dL, $P = 1.00$);

triglyceride (HIT: 146.0 vs. CG: 153.20, P = 0.084; SBE: 137.8 vs. CG: 153.20, P = 0.037; HIT: 146.00 vs. SBE: 137.8 mg/dL, P = 1.00), HDL-C (HIT: 52.5 vs. CG: 48.57, P = 1.0; SBE: 52.20 vs. CG: 48.57, P = 0.774; HIT: 52.5 vs. SBE: 52.20 mg/dL, P = 1.00), LDL-C (HIT: 74.86 vs. CG: 81.42, P = 0.099; SBE: 66.09 vs. CG: 81.42, P = 0.002; HIT: 74.86 vs. SBE: 66.09 mg/dL, P = 0.433), BF% (HIT: 24.25 vs. CG: 27.47, P = 0.001; SBE: 25.04, vs. CG: 27.47, P = 0.001; HIT: 24.25 vs. SBE: 25.04, P = 0.194), and peak oxygen uptake level (HIT: 33.95 vs. CG: 33.84, P = 0.001; SBE: 33.64 vs. CG: 33.84, P = 0.001; HIT: 33.95 vs. SBE: 33.64 mL/kg^{-1} min^{-1}, P = 0.194) after exercise interventions. The biochemistry outcomes of the study are presented in Table 2.

Figure 1 shows the comparison of between-groups mean differences in miR15b levels. For this variable, there were significant differences between the HIT and CG groups (P = 0.001) and also between the SBE and CG groups (P = 0.002). There was no significant difference between the two studied groups.

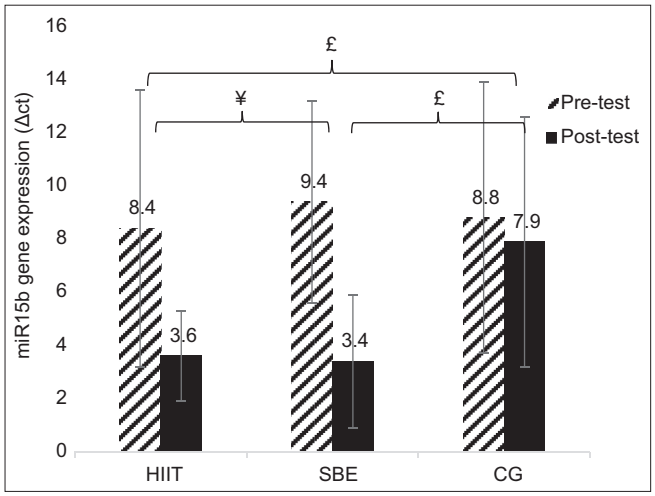

Figure 1: Changes in miR15b values among groups at two time points. CG = control group, HIT = high-intensity interval training, SBE = school-based exercise, ¥ = difference between experimental groups (P>0.05), £ = difference between experimental and control groups (P<0.05)

Discussion

The main aim of this study was to evaluate the effect of 12-week of SBE and HIT exercises on miR15b levels, body composition, peak oxygen uptake, and lipid profile adolescents with obesity. Based on our results, the proposed HIT and SBE interventions showed a significant reduction in miR15b levels (HIT: –63.8% vs. SBE: –56.7%), respectively. Previous studies aimed to investigate the effects of aerobic exercises on miR15b,[10] and miR486 expression[28] were consistent with the results of our research. The microRNAs are usually known as intracellular modulators of mitochondrial metabolism, hypertrophy, and muscle repair; therefore, these findings have attracted the attention of exercise professionals on the changes and adaptations of microRNAs as a result of exercise.[29] However, some inconsistent studies showed that exercise interventions have minor or different effects on microRNA changes. Previous studies suggested that some exercise interventions caused a reduction in miR221-3p expression in obese and overweight men and women,[30] whereas the other mode of training leads to an increase in miR214 and miR126 levels.[18]

A large number of microRNAs of specific tissues of the body are expressed during and after exercise and induce a sensory-motor response to physiological stimuli, and also the expression patterns of most microRNAs seem to be specific to the mode and intensity of training.[16] Also, it has been suggested that circulatory microRNAs released from the endothelial cells in response to increased exercise-induced shear stress could be utilized by the cells in non-active vascular tissue to facilitate cellular adaptation.[17] Therefore, one of the possible mechanisms is to reduce miR15b levels from the circulation by some other

Table 1: Characteristics of participants in pre-post tests (mean±SD)

Measured variables	Groups	Pre-test	Post-test	P (pre-post)	P (between groups)
Weight (Kg)	HIT	74.0±13.9	73.3±12.9*	0.01	0.01#
	SBE	75.1±12.0	73.9±12.2*	0.04	
	Control	74.5±13.7	74.8±13.5	0.394	
BMI (Kg/m^2)	HIT	26.2±2.3	25.5±1.7*	0.007	0.01#
	SBE	26.8±2.2	25.5±2.5*	0.01	
	Control	26.2±2.5	26.9±2.4	0.424	
Body fat (%)	HIT	27.2±3.6	24.2±2.9*	0.001	0.01#
	SBE	27.0±3.8	25.0±2.8*	0.001	
	Control	27.3±3.6	27.4±3.7	0.372	
VO_{2peak} (mL/kg^{-1} min^{-1})	HIT	32.6±2.3	33.9±2.9*	0.016	0.024#
	SBE	32.6±2.8	33.6±2.6	0.036	
	Control	32.0±1.5	31.8±1.5	0.480	

Abbreviations: mean±SD (P<0.05). *Differences between time points within the conditions (pre-post), #differences between the control group, £differences between experimental groups, CG=control group; HIT=high-intensity interval training, SBE=school-based exercises; BMI=body mass index; BF=body fat; VO_{2peak}=peak oxygen uptake

Table 2: Mean (±SD) of physiological and biochemical variables before and after 12 weeks in the studied groups

Variables	SBE (*n*=13)			HIT (*n*=13)			CG (*n*=12)			*P* (Between groups)
	Pre-test	Post-test	*P* (pre-post)	Pre-test	Post-test	*P* (pre-post)	Pre-test	Post-test	*P* (pre-post)	
miR15b (ΔCt)	8.35±5.2	3.61*± 1.7	0.007	9.44±3.8	3.41* ± 2.5	0.001	8.81±5.1	7.91±4.7	0.263	0.01#
Cholesterol (mg/dL)	151.92±24.6	137.80*± 25.1	0.005	160.07±23.40	146.00±24.5	0.001	153.93±19.5	153.20±17.6	0.425	0.025#
Triglyceride (mg/dL)	95.76±41.8	87.76±31.0	0.281	110.38±41.16	91.69±29.0	0.029	106.53±27.5	106.00±23.6	0.859	0.134
HDL (mg/dL)	49.83±11.6	52.20±12.7	0.437	50. 89±10.63	52.50±11.9	0.637	49.54±10.9	48.57±10.4	0.419	0.479
LDL (mg/dL)	83.48±23.9	66.09*±23. 6	0.001	86.18±17.82	74.86* ± 20.8	0.010	82.54±20.4	81.42±18.7	0.708	0.003#

Data are mean±SD; $P<0.05$, *Differences between time points within the conditions (pre-post), #differences between the control group, differences between experimental groups, CG=control group, HIT=high-intensity interval training, SBE=school-based exercises; LDL=low-density lipoproteins, HDL=high-density lipoprotein; ΔCt=difference in the expression between two genes, mg/dL=milligrams per deciliter

receptor cells. Another possible mechanism is the effect of exercise-induced oxidative stress, hormonal-mechanical, and osmotic changes that eliminate some of the factors in the blood and leads to the degradation of microRNAs by RNases;[31] thus, miR15b degradation with exercise may be accelerated.

Adipose tissue is one of the important sources of microRNAs that can adjust the expression of some genes in distant tissues.[32] The expression of miR15b has been shown to be enriched specifically in the adipose tissue. It has been recently suggested that adipose tissue might be a significant cause of increased serum microRNA levels in obese children.[12] Another potential mechanism is that exercise training reduces adipose tissue volume, and therefore, less mir15b is expressed by adipocytes and secreted into the blood serum.

Statistical analysis of data also showed that HIT and SBT significantly reduced total cholesterol (HIT: –8.8 vs. SBE: –9.3%) and LDL levels (HIT: –13.1 vs. SBE: –20.7%). Although there were improvements in triglyceride (HIT: –16.9 vs. SBE: –8.3%) and HDL levels (HIT: 3.1 vs. SBE: 4.8%) in both training groups, such changes were not significant that may have been attributed to the small number of subjects in this study.

The present findings seem to be consistent with previous studies that reported that exercise interventions caused no significant changes in HDL levels.[33] Other studies have also shown that the intensity of physical activity is also essential.[34] Conversely, it has been demonstrated that changes in the levels of cholesterol and LDL have been induced by the removal of fatty acids from the blood resulting from elevated lipoprotein lipase and decreased hepatic lipoprotein B after exercise training.[35]

This study has certain limitations that should be considered. First, we could not control the participants' nutrition, and heart rate during exercise; such control could have provided more accurate information. Second, we only selected obese adolescents from one city; the results, thus, could not be easily generalized to other populations. Third, all participants in this study were male adolescents, therefore, it is suggested to use both sexes in future studies and compare the results. As the present study is one of the few studies that have examined the impacts of SBE exercises in obese adolescents, further studies could shed light on different aspects of the problem under investigation.

Conclusions

Recent studies suggest that some circulating microRNAs are essential diagnostic markers for obesity-related diseases such as childhood T2DM.[36] Our results indicate that both exercise interventions with different molecular pathways may modulate the expression of mir15b and have relatively similar effects. Therefore, we conclude that various

exercise interventions, especially school-based training strategies that could be implemented in schools and other environments may have an essential role in the prevention and management of obesity in adolescents. Additionally, because the execution of HIT exercises in adolescents with severe obesity may be difficult, and also may cause some injuries, we recommend a variety of SBE training programs.

Ethical approval

This study approved by the Ethics Committee of the University of Isfahan under the ethics code of IR.UI. REC.1399.054 with adherence of Helsinki ethical principles. (IRCT20200515047455N1).

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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