ORIGINAL ARTICLE

Nr 2025;15 (1):107-112

Circulating Levels of microRNA-122 and Weight Change in Response to Combined Exercise Interventions In Metabolic Syndrome

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DOI:
10.32098/mltj.01.2025.12

LEVEL OF EVIDENCE: 1C

SUMMARY

Background. The study aimed to assess the combined exercise effects of the Circulating Levels of microRNA-122 and weight Change in men with metabolic syndrome (MeS).

Methods. Forty men with MetS according to International Diabetes Federation criteria were randomized interventional and control groups. We investigated the effect of 12 weeks combined exercise on Levels of microRNA-122 and weight Change in this patients. Statistical analyzes were performed by independent t-test and paired t-test for continuous variables with normal distribution and Mann–Whitney, and Wilcoxson test for continuous variables with abnormal distribution.

Results. The results of the independent t-test and Mann–Whitney test showed that significant differences were observed between the two groups on the post-test in miRNA-122 ($p < 0.001$), BMI ($p = 0.023$), HbA1c ($p < 0.001$), TG ($p = 0.015$), HDL ($p = 0.029$), LDL ($p = 0.043$), and waist circumference ($p = 0.029$). In addition, in the intervention group, there were significant differences between pre and post-test in all of the studied variables ($p < 0.05$).

Conclusions. Our findings suggest that the protective effect of exercise might be due in part to reduced Levels of microRNA-122 and weight in metabolic syndrome and its components. Studies with larger sample sizes are warranted to confirm this hypothesis.

Study registration. The research protocol was registered on the Iranian clinical trial registration website under the code of IRCT20170114031921N1.

KEY WORDS

microRNA-122; weight; combined exercise; metabolic syndrome.

INTRODUCTION

Metabolic syndrome includes a set of metabolic disorders that put the patient at risk of coronary and diabetes diseases. The main manifestations of metabolic syndrome of central obesity, hyperglycemia, include a decrease in HDL cholesterol, hyperglycemia and hypertension (1).

The most challenging aspect of defining metabolic syndrome is waist size. The intra-abdominal environment (visceral adipose tissue) has a great relationship with insulin resistance and the risk of diabetes and coronary artery diseases, and with any waist size, the distribution of adipose tissue between subcutaneous tissue and visceral reserves is very variable (2). The most challenging aspect of defining metabolic syndrome is waist size. The intra-abdominal environment (visceral adipose tissue) has a great relationship with insulin resistance and the risk of diabetes and coronary artery diseases, and with any waist size, the distribution of adipose tissue between subcutaneous tissue and visceral reserves is very variable. Thus, in different populations with similar waist sizes, the risk is low or high. The existence of these differences among different people in the range of waist sizes is a reflection of the level of risk in different geographical locations (3). Further industrialization of the world is associated with increasing rates of obesity, and a predictable increase in the prevalence of metabolic syndrome especially in the elderly population (4).

In addition, the increasing prevalence and severity of obesity among children reflects the metabolic syndrome in the younger population, which today is estimated to be up to 12% and 30% among obese and overweight children, respectively (5). According to the studies, waist circumference increase in women and fasting hyperglycemia (< 150 mg/dl) and decrease in HDL cholesterol level and hyperglycemia are more in men (1). Several studies have shown that miRNAs play an important role in the pathogenesis of complex diseases such as insulin resistance, dyslipidemia, and cardiovascular diseases (3).

Numerous studies have proven that miRNAs are expressed in various tissues and cell types. Furthermore, the role of miRNAs in the regulation of metabolic pathways important for adipose differentiation, energy homeostasis, lipid metabolism, insulin secretion and glucose-induced inflammation has been demonstrated. Therefore, dysregulation of miRNA expression affects a variety of important cellular functions, including cell cycle regulation, apoptosis, and differentiation, and has a significant effect on health and disease development (4).

Dysregulation of microRNA as key regulators of gene expression has been reported in many diseases including diabetes. MiRNA-122 is predominant in the liver and is suggested to play a major role in regulating lipid and glucose metabolism. According to studies, MicroRNA-122 plays a role in regulating obesity and insulin resistance (6). Children with metabolic syndrome, insulin resistance and high fat mass had higher levels of miR-122 (5). Inhibition of MiRNA-122 in mice causes the oxidation of fatty acids, reduces fat synthesis and, as a result, leads to the lowering of total cholesterol (7). In humans, it has been suggested that miRNA-122 may have adverse metabolic effects and may be associated with metabolic diseases (8). Overweight/Obesity Although the metabolic syndrome was first described in the early 20th century, the global epidemic of overweight/obesity has been responsible for the recent recognition of this syndrome(6). Central fat is the main manifestation of this syndrome, indicating the fact that a strong correlation between waist size and increased body fat is responsible for the prevalence of this syndrome (9). Many symptoms of metabolic syndrome originate from lack of physical activity (10). Exercise intervention is strongly recommended to manage metabolic diseases (11). The first treatment approach for these patients is weight loss. With weight loss, there is at least a 5% to nearly 10% improvement in insulin sensitivity, often accompanied by favorable changes in many symptoms of metabolic syndrome (10, 12). Based on the studies conducted, the combined training program in the training program groups obtained significant effects on body fat, we performed this training program (13). According research combined aerobic and resistance exercise are sufficient to provide beneficial effects in subjects with Type 2 diabetes mellitus and metabolic syndrome(14-16)**,** but there was limited studies have been conducted to investigate the effect of these two types of exercise on the level of MicroRNA-122 in people with metabolic syndrome. Therefore, the aim of this study is to investigate the effect of 12 weeks of combined exercises on the level of MicroRNA-122 and the change in weight and waist circumference of men with metabolic syndrome.

MATERIALS AND METHODS

The research proposal was approved by the Ethics Committee affiliated with Hamadan University of Medical Sciences (decree code: IR.UMSHA.REC.1401.145).

Eligible patient is selected to enter the study (40 men aged 45-65) by referring to the diabetes center of Imam Hossein Hospital. At first, people were examined by a physician for their heart condition and low risk for physical activity. These patients have Systolic blood pressure (more or equal than 130 mmHg), diastolic blood pressure more or equal than 85 mmHg), triglyceride levels higher than 150 mmHg. grams/dL, fasting sugar more than 100 mg/dL, and central obesity (Waist size greater than 102 cm in men) (17). The main exclusion criteria in the trial included serum creatinine ≥ 2 mg/dL, liver dysfunction, active cancer, physical activity or inability to participate in physical activity or participate in another research design and failed to attend it for three consecutive sessions. After receiving the consent form from the patients and maintaining the confidentiality of their information, patients are blocking randomization divided into 2 groups of 40 patients, combined exercise and control groups. The men of group of combined exercises will go to Club for sports training. In the group of combined exercises (resistance-aerobic), were performed a 12-weeks aerobic program include three training sessions per week and about one hour per day, which includes running on a treadmill. In this exercise group, subjects with 55% of maximum heart rate for 25 minutes (first 2 weeks), 55 to 65% of maximum heart rate for 35 minutes (second 2 weeks), and 65 to 75% of maximum heart rate for 40 minutes (the last 4 weeks) practiced. Before starting the exercise, the subjects warm up for 10 minutes with stretching and stretching movements, and at the end of the exercise, they cool down with stretching movements for 10 minutes. Also, the maximum heart rate of the subjects is obtained through the *age - 220* formula, and the intensity of exercise will be adjusted according to the desired percentage of maximum heart rate. The resistance exercises that are done with bodybuilding machines for 12 weeks and three sessions a week include: three sets of eight exercises with the fly rack machine (Pec Deck), cable machine, front leg machine, barbell and barfix. The level of perceived exertion will also be measured every three minutes during the training session using the Borg (Borg rating of perceived exertion scale) (6-20). All the above measures are performed under the supervision of a physician, and in case of any complications, the patient's activity is immediately stopped, vital signs are checked, and if necessary, the necessary measures are taken to continue the treatment. Sampling is done in the form of pre-test and post-test; the first stage is taken one day before the exercise program and the second stage is taken 48 hours after the last training session and 7-8 hours of fasting. Whole blood EDTA is received in the amount of 3 ml per appointment.

Samples

3 ml whole blood samples were obtained from 40 men suffering from metabolic syndrome before and after eight weeks of combined exercise, referring to Imam Hossein Hospital (Hamadan), blood centrifuged at 3,000 g for 10 minutes, then serum was immediately kept at -80 °C until the experiment.

Total RNA extraction and cDNA synthesis

A total RNA extracted from serum of 40 patients by using the RNX-Plus kit (SinaClon, Iran) According to the instructions of the manufacture. Then RNA purification, qualification, concentration and absorbance at 260 and 280 nm wavelengths was investigated by a Nano Drop spectrophotometer (Thermo Fisher Scientific, USA) and electrophoresis was performed on a 1% agarose gel. cDNA synthesis was carried out using the kit of (Anacell, Iran) company based on the kit of the mentioned company, after that incubated at 37° for 60 min, and 70° for 5 min by thermal cycler (Bio-Rad, USA), then chill on the ice or at 4c.

Expression of mir-122 by Real-time polymerase chain reaction assay

The cDNA was synthesized from RNA by cDNA synthesis kit (Anacell teb, Iran), then real-time PCR was performed for miRNA-122, as the target and u6, as the housekeeping gene on the Light Cycler® 96 (Roche, Germany). Pursuant to the Syber Green master mix and specific primers (Anacell teb), A total volume of the reaction was 20 µl PCR reaction, which included 6 µl distilled water, 10 µl master mix, 2 µl cDNA, and 1 µl each primer. The amplification program was designed according to the appropriate annealing temperature: 1 cycle at 95 °C for 900 seconds, followed by 40 cycles of denaturation at 95 °C for 15 seconds, annealing at 60 °C for 30 seconds, and 72 °C for 30 seconds, the last cycle, and melting curve was utilized to detect product specificity. The fold change of mir-122 expression levels was calculated by using the 2-ΔΔCt formula.

Statistical analysis

The normality of the continuous variables was assessed using the Shpiro-Wilk test. Statistical analyzes were performed by independent t-test and paired t-test for continuous variables with normal distribution and Mann-Whitney, and Wilcoxson test for continuous variables with abnormal distribution. All analyses were done using SPSS software version 24. All significance levels were considered less than 0.05.

RESULTS

In this study, 40 men with metabolic syndrome between the ages of 45 to 65 years were included. Participants were included in two intervention and control groups. The characteristics of men with metabolic syndrome are given in **table I**. In order to compare the effect of combined exercises on BMI, HbA1c, TG, HDL, LDL, waist circumference, and miRNA-122 in men, an independent t-test or Mann-Whitney test was used to determine the differences between groups in the pre and post-test. The results showed that significant differences were observed between the two groups on the post-test in miRNA-122 ($p < 0.001$), BMI ($p = 0.023$), HbA1c ($p < 0.001$), TG ($p = 0.015$), HDL ($p = 0.029$), LDL ($p = 0.043$), and waist circumference ($p = 0.029$). In the pre-test stage, there were no significant differences between the two groups ($p > 0.05$).

Also, the comparative pre and post-test results in each group using a paired t-test or Wilcoxson test are presented in **table I**. According to the results, there were no significant differences between pre and post-test in the control group ($p > 0.05$). However, in the intervention group, there were significant differences in all of the studied variables ($p < 0.05$).

DISCUSSION

This study aimed to evaluate the effects of 10 weeks of a combination of aerobic and resistance exercises on the serum levels of miRNA-122, weight, and lipid profiles in men with MetS.

The main finding of this randomized controlled trial was that implementing a course of combined exercises to reduce the risk factors of heart and metabolic diseases improves the level of miRNA-122 in men with metabolic syndrome. miRNAs can be modified by environmental factors or external stimuli, such as physical exercise (18). Limited studies have investigated the effect of various types of physical activity on miRNA-122 serum levels. By regulating the level of gene expression through post-transcriptional mechanisms, miRNA-122 plays an important role in various biological processes, and their level changes are associated with lipid and glucose metabolic disorders. Based on the studies, it has been suggested that miR-122 plays a central role in the regulation of blood glucose metabolism and the development of diabetes mellitus (19). Approximately 75% of the total liver miRNA expression belongs to miRNA-122, which is the most abundant miRNA in the liver. miR-122 plays an essential role in maintaining liver function through the regulation of gene expression and reduces total cholesterol, HDL, apolipoprotein, LDL and apolipoprotein B levels (20). In this study, the exercise program in the intervention group compared to the control group was seen after, a significant decrease in lipid factors, which can be justified considering the role of miR-122. In fact, it is assumed that

Table I. The characteristics of men with metabolic syndrome.

Stage	Variables	Group		P-value
		Control (n = 20) Mean ± SD	Intervention (n = 20) Mean ± SD	
MirRNA-122	Pre-test	30.34 ± 2.30	30.29 ± 2.31	0.946
	Post-test	30.05 ± 2.63	27.33 ± 1.50	< 0.001
P-value		0.631	< 0.001	
BMI (kg/m)	Pre-test	27.84 ± 2.02	27.80 ± 2.85	0.965
	Post-test	27.76 ± 2.06	26.08 ± 2.38	0.023
P-value		0.247	< 0.001	
HbA1c (%)	Pre-test	8.00 ± 0.63	7.98 ± 0.66	0.946
	Post-test	7.97 ± 0.59	7.33 ± 0.44	< 0.001
P-value		0.150	0.004	
TG (mg/dl)	Pre-test	197.00 ± 14.64	198.25 ± 14.93	0.791
	Post-test	196.85 ± 13.31	186.30 ± 12.98	0.015
P-value		0.820	< 0.001	
HDL (mg/dl)	Pre-test	43.35 ± 3.75	43.80 ± 4.09	0.719
	Post-test	43.65 ± 3.51	46.30 ± 3.88	0.029
P-value		0.055	< 0.001	
LDL (mg/dl)	Pre-test	113.75 ± 11.73	113.80 ± 12.21	0.990
	Post-test	112.80 ± 12.28	105.50 ± 9.56	0.043
P-value			0.242	
Waist circumference	Pre-test	108.95 ± 6.49	110.25 ± 7.21	0.553
	Post-test	108.75 ± 6.45	103.80 ± 7.17	0.027
P-value		0.163	< 0.001	

SD: Standard deviation; TG: Triglycerides; HDL: High-density lipoprotein cholesterol; LDL: Low-density lipoprotein cholesterol.

physical exercise has multifactorial benefits by reducing intrahepatic TG accumulation on metabolic disorders and leads to improved insulin sensitivity and reduced oxidative stress and recommended treatment for obesity and diabetes (21). The results of Li *et al.* study's showed that after ten weeks of combined exercises in metabolic syndrome index according to exercise dose in obese male college students, triglyceride and high-density lipoprotein-cholesterol levels, fasting blood glucose levels, waist circumference showed a significant decrease, but blood pressure did not change (22). Also, in this study, the results showed that there was a significant weight loss in the intervention group compared to the control group. The study of Wang *et al.* showed that obese people had a higher level of miRNA-122 than the control group (non-obese) (23). In fact, after the exercise protocol, miRNA-122 levels decreased in the intervention group, and weight loss was also observed, which can justify the relationship between weight loss following miRNA-122 level reduction. Several studies have reported a positive correlation between miR-122 and BMI (23, 24). Regarding the absolute effect of exercise on gene expression 122-miR, Castaño *et al.* reported a decrease in 122-miR levels in liver tissue and skeletal muscle following five weeks of high-intensity interval training (22 m/min) (25). In fact, there is a significant negative relationship between the level and improvement in metabolic syndrome. The results of this study support the reduction of miR-122 levels following weight loss. which was consistent with the results of the study of Anne Lundby Hess (3). Krützfeldt *et al.* suggested that aerobic exercise without caloric restriction will reduce visceral fat (more than 30 cm^2) and symptoms of metabolic syndrome (26). Discrepancies in results may result from differences in intervention methods, intervention period, or miR-122 blood sources among studies. However, further studies are necessary to assess whether measuring circulating miR-122 levels can contribute to current methods of developing metabolically unhealthy overweight or obesity. Although recent studies have suggested the potential of circulating miRNAs as a tool to enhance the understanding of obesity-related metabolic complications, we were only able to link one of the 20 miRNAs tested with weight loss or other metabolic-mediated variables.

Study strengths and limitations

The strength of our study was to perform a combined exercise program to investigate the relationship between miRNA-122 and changes in weight and abdominal circumference. This study has several potential limitations. First, the generalizability of the study findings could be limited because our study examined only one area. Second, in order to avoid the influence of hormonal factors, conducting the study in men and finally, our results may not be generalized to other populations because the participants were male. Therefore, more research is needed to confirm our results using longer exercise interventions and larger groups.

CONCLUSIONS

Our findings suggest that the protective effect of exercise might be due in part to reduced Levels of microRNA-122 and weight in metabolic syndrome and its components. Studies with larger sample sizes are warranted to confirm this hypothesis.

FUNDINGS

This research was supported under a research grant (grant no.: 140104282929) from Hamadan University of Medical Sciences, Iran. The study funder had no role in study design, data collection, writing of the manuscript, and submission.

DATA AVAILABILITY

Data are available under reasonable request to the corresponding author.

CONTRIBUTIONS

HN, FM, AH: project administration, investigation, writing – original draft. RNV, HN, SSH: writing – review & editing.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

ACKNOWLEDGEMENTS

The authors would like to thank the participation of the men in this study and the Core Facility Laboratory, Hamadan University of Medical Sciences.

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