Original Article

The Effect of All Extremity High Intensity Interval Training on Athero-Protective Factors and Endothelial Function in Overweight and Obese Women

Abstract

Context: Obesity is associated with endothelial dysfunction and cardiovascular diseases. Adiponectin and fibroblast growth factor 21 (FGF21) as hormones are highly contributive in cardiovascular system, while they are disrupted through obesity. Weight-bearing high intensity interval training (HIIT) as an effective procedure in preventing obesity-related complications in adults with obesity may be limited due to the subjects' muscular weakness and complications interfering walking. **Aims:** The purpose of this study was to assess the effectiveness of non-weight bearing all extremity HIIT (all ex. HIIT) on FGF21, adiponectin, nitric oxide (NO), and flow mediated dilation (FMD) in overweight and obese women. **Methods:** Thirty healthy overweight and obese sedentary university female students within 20.53 ± 1.50 age range and BMI ≥27 kg.m^{-2} were assigned in two experimental and control groups. All ex. HIIT consisted of 4 × 4 min at 85–90% max HR with an interspersed with 3 × 3 min recovery per round at 70% max HR by upper and lower ergometers in a simultaneous manner on 10 weeks of four sessions of 40 min each. FGF21, adiponectin, NO, FMD, weight, waist and maximal oxygen uptake (VO_{2max}) were measured in pre and post-tests. Paired sample *t*-test and analysis of covariance are applied for statistical analysis. **Results:** Results indicated a significant increase in adiponectin ($P \leq 0.01$) and FMD ($P \leq 0.001$), while there existed no changes in FGF21 at ($P \geq 0.10$) and NO ($P \geq 0.84$). The weight and waist decreased at ($P \leq 0.001$), and the VO_{2max} increased at ($P \leq 0.001$). **Conclusions:** All ex. HIIT may be a safe alternative for overweigh and obese women who have complications with weight-bearing exercises, and may increase adiponectin, and improve the FMD, aerobic fitness, and body composition.

Keywords: *Adiponectin, atherosclerosis, fibroblast growth factor 21, high intensity interval training*

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Introduction

Obesity constitutes one of the major risk factors for non-communicable metabolic diseases.[1] Metabolic disorders like diabetes, insulin resistance, and cardiovascular disease are not a simple dysfunction of the local organs, instead they are uncoordinated among hormones productions in different organs.[2] Adipose tissue and liver are the highly active endocrine organs that secrete bioactive molecules which are highly contributive in regulating body energy metabolism and cardiovascular tone.[3] Adiponectin and FGF21 constitute the two major hormones secreted from adipose tissue and liver respectively.[4,5] In spite of their production sources and structures, both the hormones are contributive in decreasing lipid and glucose,[6,7] and protecting cardiovascular system.[8]

Assessment of adiponectin/FGF21 by administration or genetic manipulation has revealed an increase in energy expenditure, a decrease in the insulin resistance and atherosclerosis.[9,10] The FGF21 decreased atherosclerosis through adiponectin induction,[8,11] while adiponectin alleviated endothelial function by an increase in NO production through adenosine monophosphate-activated protein kinase (AMPK) pathway.[12] There exist studies on presence of FGF21–adiponectin axis in regulating vascular and metabolic homeostasis, while as to this axis in obesity they revealed some distortion.[13,14] FGF21 is high, and adiponectin is low in obese than normal weight people.[4,15]

According to the meta-analyses run by[16], the traditional exercise training including resistance, continues or circuit trainings improved FMD by 2.3%, while it is

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revealed in many studies that weight-bearing HIIT had impressive effect of cardiovascular function in relation to traditional moderate intensity trainings in obesity.[17-19] On the other hand slow walking, dyspnoea, foot and ankle pain and lower muscular weakness due to obesity make weight-bearing HIIT exercise difficult.[20] Non-weight bearing all ex. HIIT may be an appealing modality to compensate the lower extremity fatigue and activates many muscles.[21] To the best knowledge of the author here, as the obesity, there exist no assessment on this type of training. The objective of this study was to assess the effect of non-weight bearing all ex. HIIT on FGF21, adiponectin, NO and the athero-protective effect thereof, in overweight and obese women.

Methods

This study was extracted from a dissertation and was a cross-sectional semi-experimental study approved by the Research Committee of the University of Isfahan, Iran according to the policy of the Ethics Committee of University of Isfahan code: 1396.041. The statistical population here consisted of 30 female university students within 18–23 age range, selected in experimental and control groups equally. All were of sedentary (exercise ≤2 times/week), overweight or obesity, with body mass index (BMI) ≥27 $kg.m^{-2}$, free of CVD, diabetes, hormonal complications, medication consumption, smoking, with no restricted diet. Participants responded to a medical history questionnaire and signed a written consent for participating in this experiment prior to data collection. The following procedures were applied to materialize the objective here.

Testing assessment

The baseline measurements were made after 12 h fasting. The post-test measurements were made 48 h after last session of training at the fasting state to eliminate acute effect of the exercise. In day 1 the weight and height were measured with the least cloths on, on Seca scale and stadiometer (model 220, Germany). Waist (level of iliac crest) was measured by standard tape. After 20 min rest in sitting position the pulse meter (Polar F4, Finland) was applied to register resting heart rate (HR). To estimate the body composition, calliper (Lange, Korea) was applied to measure skin fold in three sides abdomen, ilium, and triceps.[22] To assess VO_{2max}, Young Men's Christian Association's (YMCA) submaximal test was run with ergometer (Monark 839 Sweden).[23] In day 2, after 12 h fasting, 10_{cc} of venues blood was collected and centrifuged 4,000 rpm for 20 min. The serum was gathered and stored in -80°C. The FGF21 [R&D systems, Quanticine, "enzyme-linked immunosorbent assay (ELISA), USA], adiponectin (Bio legend, ELISA MAX Deluxe Set, USA), and NO (abcam, colorimetric, UK) kits are applied in this analysis according to manufacture instructions.

Measurement of FMD

FMD was measured after 72 h during which no medication, and vitamin supplement were consumed. A 12 h restriction was assigned in consuming alcohol, caffeine, high fat, and high carbohydrate diet and vigorous exercise. The FMD was measured at phase one of menstruation days 1–7, with high resolution ultrasound machine (Vivid 3, GE Health care, USA) and a linear array probe (10 MHZ).[24] The measurement was made at the end of diastolic phase identified by R wave on electrocardiography. The initial measurement of brachial artery diameter was made after 20 min resting in supine position at 22–24°C in about 3 cm above antecubittal fossa. Following this, one cuff fixed at 8 cm of brachial artery distal was inflated to 250–300 mmHg for 5 min. The arterial baseline diameter was measured before cuff inflation and 2 min after cuff deflation in the same point. FMD% was calculated through the following equation:

$$\text{FMD\%} = \frac{\text{Peak diameter} - \text{baseline diameter}}{\text{baseline diameter}} \times 100$$

Recorded daily physical activity and diet

All subjects were instructed to maintain their normal daily physical activity and diet during the study period. Their daily physical activities except all ex. HIIT program was measured through pedometer (iHealth Edge, USA) at base line, 5^{th} and 10^{th} weeks for three times: two weekday and one weekend day. The mean of three daily activities in each series was calculated and compared between and within both the groups. To calculate the calorie intake, the subjects were asked to report volume of food and drink intake according to the above interval, in a 3-day diet record. Energy intake was determined by applying the diet analyzer software NUT-4 modified by inserting the Iranian Food Table.[25] The mean of three daily calorie intake in each series was calculated and compared between the between and within the both groups.

Exercise training

The peak HR was determined by 220-age. All ex. HIIT group were exposed to 4 × 4 min at 85–90% max HR interspersed with 3 × 3 min recovery per round at 70% max HR.[26] The upper body ergometer (Monark 831E) and lower body ergometer (Monark 839E) were applied in a simultaneous manner on 10 weeks of four sessions of 40 min each. The first week was considered as the familiarization and preconditioning phase, after which the intensity and duration of training were increased to reach the target peak HR and total time of 40 min.

Statistical analyses

All statistical analyses were run in IBM SPSS Statistics version 22 software. Shapiro–Wilk test was applied to assess the normality of data distribution. Non-normally data was subjected to logarithmic transformation. Levine's test was run to indicate homogeneity of variances. The Pair sample *t*-test was run to compare pre- and post-interventions within the groups. Analysis of covariance (ANCOVA) with pre-test score as covariate and Mann–Whitney U test were run to assess differences in parametric and non-parametric data, respectively. Repeated measure ANOVA was applied for calorie intake and Krouskal–Wallis test was run for daily physical activity analyses. Quantitative variables was expressed as the mean ± SD. Power calculation was based on primary outcome of FMD%. According to statistical power 0.8 and level of significance ($\alpha = 0.05$) for detection of effect size 15% introduced by[27], to determine the FMD% from pre- to post-HIIT, at least eight individuals in each group are needed.

Results

Of the 30 participating subjects, 4 (13%) did not complete the intervention. The reasons of withdrawal consisted of: schedule conflict (3 subject) and exercise induced asthma in high intensities of HIIT (1 subject). At first sessions it was hard to coordinate the arms and legs during upper and lower ergometers operation in a simultaneous manner, which was resolved over time. There was no significant differences in all variables at baseline [Table 1]. There were no changes in daily physical activity ($P = 0.95$) and daily calorie intake ($P = 0.88$) between the groups. No significant changes were observed in both the groups as to FGF21 and NO. The observed increase in the adiponectin was 6.9%, FMD was 15.6% and VO_{2max} was 19.7%. The observed decrease in the weight was 2.4%, body fat percent (BF%) was 7.2%, and waist was 3.3% after training and all variables remained unchanged in control group, [Table 2].

Table 1: General characteristics, anthropometric and blood analyses of groups at baseline

Variable	HIIT	Control	*P*
Age (yrs.)	20.23±1.30	20.69±1.70	0.60
Height (cm)	162.76±5.05	160.61±5.54	0.31
Weight (kg)	78.65±13.24	82.80±14.30	0.45
Waist (cm)	86.34±8.27	89.07±11.10	0.48
Body fat%	38.83±2.21	39.86±2.71	0.29
Log FGF21 (pg/ml)*	2.24±0.29	2.37±0.32	0.15
Adiponectin (ng/ml)	8.37±1.09	8.95±0.55	0.31
Log NO (mmol/l)*	1.68±0.17	1.60±0.29	0.35
FMD%	8.83±3.71	9.27±5.01	0.80
VO_{2max} (ml/kg/min)	28.55±3.75	30.53±5.49	0.29

Data presented as mean±SD. The *is: logarithmic transformed for non-normally distributed data. FGF21: Fibroblast growth factor 21, NO: Nitric oxide, FMD: Flow mediated dilation VO_{2max}: maximal oxygen uptake

Table 2: Effect of all ex. HIIT on blood variables, endothelial function, aerobic power and body composition

Variable	Group	Pre	Post	P^1	P^2
Log FGF21 (pg/ml)*	All ex. HIIT	2.24±0.29	2.23±0.39	0.9	
	Control	2.37±0.32	2.36±0.34	0.06	0.93
Adiponectin (ng/ml)	All ex. HIIT	8.37±1.09	8.95±0.55	0.05	
	control	8.92±1.57	8.77±1.48	0.26	0.01†
Log NO (mmol/l)*	All ex. HIIT	1.68±0.17	1.66±0.22	0.77	
	Control	1.60±0.29	1.60±0.19	0.66	0.84
FMD%	All ex. HIIT	8.83±3.71	10.21±3.73	0.02	
	Control	9.27±5.01	8.07±4.06	0.02	<0.001
Weight (kg)	All ex. HIIT	78.65±13.24	76.69±13.13	<0.001	
	control	82.80±14.30	83±14.05	0.48	<0.001
%Body Fat	All ex. HIIT	38.83±2.21	36.22±3.21	<0.001	
	Control	39.86±2.71	40.24±2.92	0.15	<0.001
Waist (cm)	All ex. HIIT	86.34±8.27	83.59±7.71	<0.001	
	Control	89.07±11.10	89.40±10.64	0.29	<0.001
VO_{2max} (ml/kg/min)	All ex. HIIT	28.55±3.75	34.19±4.09	<0.001	
	Control	30.53±5.49	30.74±4.80	0.78	<0.001

P^1 is the paired *t*-test. The *is Logarithmic transformed for non-normally distributed data P^2 is the ANCOVA output adjusted by baseline results. The † is the Mann Whitney U test. $P \leq 0.05$. FGF21: Fibroblast growth factor 21, NO: nitric oxide, FMD: Flow mediated dilation VO_{2max}: maximal oxygen uptake

Discussion

This study demonstrated that all ex. HIIT would be feasible and well tolerated for overweight and obese women who have complication with weight bearing exercise. This was based on 86% completion rate for this training mode. The daily physical activity and daily calorie intake of the subjects remained unchanged, therefore, it was speculated that changes in variables were only related to exercise training.

In this study the effect of all ex. HIIT on the athero-protective effect of FGF21, adiponectin, FMD, NO, aerobic fitness, and weight management of women with overweight and obesity were assessed. The observation of experiment period revealed that serum FGF21 and NO remained unchanged, adiponectin level increased, FMD and Vo_{2max} improved and weight, BF% and waist decreased. As mentioned this was the first study run in assessing the effect of all ex. HIIT on overweight and obese women. Due to uniquenessof this study where the focus was on all ex. HIIT on overweight obese women, there existed no study to which this article could be compared with, while because of necessity the studies run on HIIT were mentioned here.

Despite to assessment run on metabolic effects of FGF21 in human, there existed few studies run on this hepatocyte in cardiovascular disease. No significant changes in FGF21 was observed in this study. In only one available study, it was reported that 3 months combined exercise program decreased FGF21 in young obese women.[28] An increase in FGF21 after exercise in young women was found in[29]. These discrepancies between this and the available studies may be explained by the obesity status, age of subjects, or differences in exercise training programs and duration.

Here a significant increase in adiponectin was observed after intervention with respect to weight, waist, and BF% reduction. According to available studies weight decreased and adiponectin level increased after weight bearing HIIT or aerobic training in obese women.[30-33] On the other hand six months of aerobic exercise had no changes in weight and subsequently adiponectin level in obese patients.[34] It is deduced that any loss in weight and body fat to a certain degree is necessary in affecting adiponectin level in obesity. In this study a reduction in weight, BF%, and waist circumferences were significant with non-weight bearing all ex. HIIT and these were probably the reasons of increasing adiponectin. Recently such findings are reported[35] as well. Adiponectin has an anti-atherogenic and anti-inflammatory effect by activation AMPK that lead to endothelial NO production and alleviate endothelial dysfunction and prevent atherosclerosis.[12]

In this study all ex. HIIT improved endothelial function assessed by FMD in a significant manner, while the plasma NO level remained unchanged. Improvement of FMD due to all ex. HIIT could be an important result in preventing atherosclerosis and CVD in obesity. The claim by Ramos JS *et al.*[19] stated that HIIT was an affective program for FMD and the findings by Sawyer BJ *et al.*[36] were in correspondence with this study. Some studies revealed no changes on FMD after HIIT.[37] These differences might be due to the age of the subjects or the type and duration of the exercise programs. One of the most important mechanisms of exercise-induced FMD improvement is the shear stress and NO production.[38] It is possible that exercise subject to another mechanisms independent of NO could improve the endothelial function which could be related to weight loss. In this study weight and BF% and waist decreased significantly. It was deduced that all ex. HIIT could decrease both the subcutaneous and visceral fat, where the latter is more important factor in preventing CVD risk. One of the reasons in weight and fat reduction in this study was the involvement of large muscle mass due to activation of upper and lower body in obese women. This might be due to both the exercise and post-exercise fat oxidation increase caused by resynthesized adenosine three phosphate (ATP) from Phosphocreatine (PCr) and triacylglycerol in muscles.[39]

Here it was observed that VO_{2max} had a significant improvement after all ex. HIIT. Although there existed studies where due to sub-maximal aerobic test which an underestimation of VO_{2max} was evident.[40] The result observed here revealed an improvement of about 5.6 ml.kg/min in response to all ex. HIIT. This was a good result because according to the available data every 3.5 ml.kg/min improvement in aerobic power is related to 12–22% lower risk of CVD mortality.[26] The fact that VO_{2max} improved significantly due to all ex. HIIT corresponded to the findings by Hwang C-L *et al.*[26] Mechanisms underlying all ex. HIIT in increasing VO_{2max} are undetermined, but is assumed that a decrease in total peripheral resistance in vessels and constitute the reason to improve VO_{2max}.[18,19]

In this study, it was observed that the changes in VO_{2max} percentage was higher than changes in weight and body fat percentage. This revealed that implementing exercise protocol in overweight and obese subjects should not be only emphasized on weight reduction, because even at low weight reduction, the appropriate exercise by increasing VO_{2max} could be an essential factor in increasing FMD and preventing atherosclerosis and CVD.

The strength of this study consisted of: (1) being the first in assessing the non-weight bearing all ex. HIIT by upper and lower ergometers simultaneously, in overweight and obese women; (2) each exercise session was supervised by monitoring heart rate to assure the accuracy of exercise intensity; and (3) it was prescription of exercise rather than increased habitual physical activity.

The limitation of this study is consisted of: (1) The adaptation observed in this study were limited to length of this intervention which could have needed longer interventions to observe greater adaptations. (2) This intervention included only young women, and assessing the gender-specific effects were not of concern. (3) The sample size of this study was small, while larger cohorts would have produced better findings.

Conclusions

It was concluded that non-weight bearing all ex. HIIT could be appropriate for overweight and obese women having problem with weight bearing or running exercises. Although all ex. HIIT could not change FGF21 and NO, but it decreased weight, BF %, and waist, subsequently, increased adiponectin and improved FMD. The percentage of changes in VO_{2max} was greater than the same in weight and BF%, indicating that the focus of the exercise protocols for these subjects should not be only on weight loss. More studies need to clarify and assure the beneficial effect of all ex. HIIT on overweight and obese women. It is obvious that the findings here and studies alike would contribute to the prevention of the issue at hand.

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Conflicts of interest

There are no conflicts of interest.

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