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Effects of sprint interval or combined aerobic and resistance training on myokines in overweight women with type 2 diabetes: A randomized controlled trial

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ABSTRACT

Our primary aim was to assess the effects of two different training modalities: sprint interval training (SIT) or combined aerobic and resistance training (A + R) on circulating myokines related to metabolic profile and adiposity in type 2 diabetes (T2D). Fifty-two overweight women with T2D [55 ± 6 yrs., BMI 28.9 ± 4.1 kg/m^2, HbA1c 9.4 ± 0.82% (79 mmol/mol)] were randomized to SIT (n = 17), A + R training (n = 17) or control (n = 18) for 10 weeks. Myokines, metabolic outcomes, body composition and cardiorespiratory fitness were assessed at baseline and 48 hours after the last training session/control period. Relationships between myokines and other variables were investigated via linear regression models. Completion rate was 81%. There was no effect of either exercise modality on any myokine. Interlukin-15 decreased over time irrespective of group assignment (p = 0.02). Aerobic capacity (p = 0.01), fasting glucose (p = 0.03) and HbA1c (p = 0.006) improved significantly and similarly in both exercise groups compared to controls. Insulin (p = 0.02), weight (p = 0.020, body max index (BMI) (p = 0.01) decreased significantly over time irrespective of group. Changes in myokines were unrelated to changes in body composition or metabolic profile. Neither SIT or A + R training altered myokines measured 48 h after exercise in T2D, despite improving aerobic capacity and glucose homeostasis relative to controls. Future studies are needed to elucidate the time course and clinical relevance of putative myokine responses to exercise in this and other cohorts.

1. Introduction

Type 2 diabetes is a prevalent and growing epidemic, with 382 million people worldwide diagnosed with diabetes in 2013 (90% type 2 diabetes), and this number expected to rise to 592 million by 2035 [1,2]. Type 2 diabetes is characterized by a range of metabolic disturbances such as hyperinsulinemia, enhanced hepatic gluconeogenesis, impaired glucose uptake, metabolic inflexibility and mitochondrial dysfunction, and often associated with a sedentary lifestyle. Physical activity is a well-established therapeutic management for this and other chronic diseases [1]. Identification of a muscle contraction-induced humoral factor, an “exercise factor” that could mediate some of the exercise-induced changes in other organs is of great interest. Skeletal muscles produce and express cytokines belonging to distinct different families [1]. Muscle-derived IL-6 was named as the first such “myokine” [2,3]. However, recent research demonstrates that skeletal muscles may produce and express myokines belonging to distinctly different families such as Interleukin-15, Fibroblast Growth Factor 21 (FGF21), irisin, Angiopoietin-like 4 (ANGPTL4) and SPARC. These myokines are regulated by concentric muscle contractions, which have been associated with increased expression of specific mRNAs and their linked proteins [1].

These putative exercise-related myokines have been reported to differ in healthy and clinical cohorts. Some studies have shown that these myokines are higher in cohorts with cardio-metabolic disease. For example, ANGPTL4, FGF21 and SPARC concentrations have been

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reported to be higher in individuals with type 2 diabetes [6–8] compared to healthy peers. In one of these studies, FGF21 was linked to the initiation and formation of atherosclerotic plaques in the early stage of atherosclerosis in newly diagnosed individuals with type 2 diabetes [4].

There is also heterogeneity in the literature to date on the effect of exercise on these myokines. A number of studies showed no alterations in myokines levels in chronic exercise modalities, which could be due to the differences in pathophysiological states of skeletal muscle. It seems that healthy skeletal muscles secrete less myokines compared to obese people [5]. It seems that, monitoring of adipo-myokine profiles such as IL-15, SPARC, irisin, FGF-21 and ANGPTL4 [6] could provide means to maximize the health benefits of exercise training on diabetes mellitus.

For example, a 12-week trial of combined aerobic and resistance training reduced FGF21 levels in obese women [7]. However, no change was observed after eight weeks of endurance training in obese men [5], and an increase was observed after two weeks of aerobic training in sedentary young women [8]. Irisin levels doubled in healthy adults after 10 weeks of aerobic exercise [9]. Similarly, elevated circulating IL-15 levels have been reported in healthy cohorts after a single bout of resistance or endurance exercise as well as after 8 weeks of resistance training [13–15]. This heterogeneity may have been contributed to by varied modalities of exercise, gender, age, health status, as well as measurement time points utilized across these trials.

The time course of myokine activation is particularly relevant. Serum IL-15, assessed by whole genome RNA profiling of skeletal muscle gene expression, was measures in untrained healthy young men running for 30 minutes at 70% of their predicted maximum heart rate [13]. Serum IL-15 was elevated 10 minutes after the exercise but was not significant by 1 hour and had fully returned to the pre-exercise level by 3 hours. However, another study [10] reported IL-15 mRNA levels were up-regulated twofold at 24 h of recovery after a bout of resistance exercise without any changes in muscle IL-15 protein content or plasma IL-15 at 6 or 48 h post-exercise. There is little information about chronic training effects (48 + hours after the last bout of exercise). Thus, timing of myokine measurement in relation to the last exercise bout may be critical, and may have contributed to the heterogeneity referred to above.

Thus, more study is needed to determine the true role of myokines in metabolic health, the effect of various exercise prescriptions on their release, as well as the time course and clinical correlates of myokine response to exercise in diabetes and other cohorts. It is possible that previous interventions have not been robust enough in terms of modality or intensity to provoke significant, sustained elevations in myokines.

Because of complexity and variability in metabolic and molecular responses to different exercise modalities, sensitive myokines to muscle contraction could serve as promising biomarkers for monitoring improvement of body metabolism of patients with diabetes mellitus. Interestingly, increasing evidence suggested that adipo-myokines on the one hand are upregulated in the obese state, and have beneficial effects after exercise interventions on the other hand in therapeutic mechanisms [11]. It has been reported that regular exercise activates the production and release of adipokines and myokines, both of which are involved in mediating its beneficial effects on DM and insulin resistance,[3] so, we designed this study to test the effects of two theoretically-grounded, robust exercise training modalities on circulating myokines and related metabolic profiles and aerobic fitness. We hypothesized that myokines IL-15, SPARC, irisin, FGF-21 and ANGPTL4 would be increased from baseline at 48 hours after the last bout of chronic exercise training compared to a usual care control group in overweight women with type 2 diabetes. We chose to study Sprint Interval Training (SIT) because it induces more robust fitness adaptations compared to moderate intensity aerobic training [12]. We chose combined aerobic and resistance training (A + R) because this is the recommended exercise prescription for optimal metabolic benefit in type 2 diabetes [13]. Secondly, we hypothesized that both SIT and A + R would be associated with metabolic, body fat, and fitness benefits compared to the control group. Finally, we hypothesized that changes in myokines would be related to the magnitude of the metabolic, body fat and fitness benefits observed.

2. Materials and methods

2.1. Study design

We conducted a 10-week randomized controlled trial (Iranian Registry of Clinical Trials, trial registration number: IRCT20141118019995N10; http://www.irct.ir/trial/17753). The study was approved by Shahrekord University Research Ethics Committee. All participants provided written informed consent.

2.2. Participants and enrolment process

Participants were recruited from patients registered in the outpatient department of Shahrekord Hospital (Shahrekord, Iran). Inclusion criteria were: women, diagnosis of type 2 diabetes by a physician, age 30–65 yrs., 48 kg/m^2 > BMI > 25 kg/m^2, HbA1C ≥ 6.5% (48 mmol/mol), fasting blood glucose ≥126 mg/dL (7.0 mmol/l) and sedentary lifestyle. Sedentary was defined as no > 20 min structured exercise of any type per week over the past 6 months or any level of sprint interval training (SIT). Participants were excluded if they had resting blood pressure ≥ 160/100 mm Hg, fasting triglyceride ≥-5.7 mmol/L, a history of cardiovascular disease, thyroid disorder, cancer, endocrine disorder other than diabetes, kidney or liver disease, surgery, smoking or using recreational drugs or any alcohol.

The patients were randomized through block allocation with a block size of 6 by a research assistant who was not involved in this research by using a computer-generated random number sequence. Participants were stratified according to two cut-offs for each stratification of age (30–50 or 51–60 yrs), BMI (25–35 or 36–48 kg/m^2) and HbA1c (6.5–8.5% or ≥8.6%). Sequential treatment allocations were enclosed in numbered, opaque sealed envelopes, and distributed by this research assistant to each group after baseline assessment.

2.3. Exercise training protocols

Both exercise interventions were 10 weeks long. Participants exercised three times per week for 50 minutes [14] and training progressed in length and intensity (Table 1). All training was fully supervised by experienced exercise physiologists at a hospital gym, and conducted in groups of 3 to 5 participants.

2.4. Aerobic and Resistance Training Group (A + R)

Aerobic training was followed by resistance training during the same session. Participants were free to perform aerobic exercise on a treadmill or cycle ergometer. The training started with the participants warming up by cycling or treadmill for 5 min at a heart rate of < 100 beats/min. Stretching and cycling/treadmill as a cool-down with a heart rate of < 100 beats/min was performed for 10 min. Aerobic training progressed from 20 min/session at 50% maximum heart rate (HR) based on the aerobic capacity test (see below) in weeks 1–2 to 30 min/session at 70% maximum HR in weeks 3–10. Heart rate monitors (Polar T31, *Oy*, Kempele, Finland) were used to adjust workload to achieve target heart rate. The aerobic training was personalized by individualized increments. Resistance training was performed at one set of 15 max reps (maximum amount of weight that could be lifted only 15 times) with 15 repetitions for the first 2 weeks. Then intensity was increased to 2–3 sets of 12–10 max reps with 12–10 repetitions/set between weeks 3 and 10 (Table 1) [15]. All resistance training was performed on weight stack machines (DynaForce, Italy) and included the following 5 exercises: bilateral leg press, lateral pull down, bench press,

Table 1
Exercise training interventions.

Week	Resistance training					Aerobic training			SIT training		
	Set	Repetition (n)	Rest between (min)	Weight	Frequency (days/wk)	Duration (min)	Intensity (MHR %)	Frequency (day/wk)	Duration (second)	Intensity	Frequency (day/wk)
1–2	1	15	2–3	15-RM	3	15–20	60	3	4 × 30s	All-out	3
3–4	2	15	2–3	15-RM	3	25	60	3	4 × 30s	All-out	3
5–6	3	12	2–3	12-RM	3	30	70	3	4 × 30s	All-out	3
7–8	3	12	2–3	12-RM	3	30	70	3	4 × 30s	All-out	3
9–10	3	10	2–3	10-RM	3	30	70	3	4 × 30s	All-out	3

RM: Repetition maximum; MHR: Maximal heart rate; SIT: Sprint interval training.

bilateral biceps curl, and bilateral triceps push down.

2.5. Sprint training group (SIT)

The SIT training was performed on cycle ergometers (Ergomedic 894E Peak Bike, Monark EB; Varberg, Sweden) at a pedalling rate of 120 rpm. Each session consisted of a 5-minute warm-up at 25 W, 4 × 30 s maximum intensity intervals before exhaustion of the individual, each interval followed by 2 min of active recovery at 50 W.

Those participants who completed the three intervals on the first SIT session had their wattage adjusted upward by 10% increments based on performance and perceived effort, whilst for those participants unable to maintain the required minimum of 120 rpm for any interval, wattage was adjusted downwards in 10% increments based on the same criteria. During the 10 weeks of SIT if a participant completed three intervals maintaining > 120 rpm on two consecutive sessions, wattage was adjusted upward in 10% increments to ensure maximum intensity was being exerted during each training session [16].

2.6. Control group

The control group continued their usual medical care and received Farsi-translated diabetes recommendations for self-management. They were not given exercise counselling and were asked to maintain baseline activity levels during the study period.

2.7. Measurements

Pre and post assessments were conducted by the same assessor who was blind to treatment allocation.

2.8. Myokines

Baseline blood samples (10 cc) were collected from the antecubital vein in a sitting position 24 h after a 12-hour fast and before any baseline exercise testing. Post-study samples were collected 48 h after the last exercise session in the intervention groups. Samples were processed immediately and kept at −80 °C until time of analysis. Serum IL-15 (Boster Co, cat number EK0426), SPARC (Boster Co., cat number EK1210), irisin (Hangzhou Eastbiopharm Co, cat number K-E90905), FGF-21 (Boster Co, cat number EK0994) and ANGPTL4 (Boster Co, cat number EK0960) levels were measured by using commercial human ELISA kits. Pre and post samples from each participant were analyzed in the same assay, and the inter- and intra-assay coefficients of variation ranged from 7.8% to 11% for IL-15, SPARC, irisin, FGF-21 and ANGPTL4.

2.9. Metabolic profile

Fasting blood glucose was measured using glucose oxidase method kit (Pars Azmoon, Tehran, Iran), through auto-analyzer devices (Hitachi®, model 704, 902 made in Japan). Serum insulin concentrations were determined by ELISA technique using a microplate reader. Hepatic insulin resistance (HOMA-IR) was calculated with fasting glucose (mg/dL) and fasting insulin (mU/L) values using the validated calculator (accessed at. http://www.dtu.ox.ac.uk) in those participants not taking exogenous insulin (n = 22).

2.10. Aerobic capacity

The modified Bruce Protocol treadmill test was used to measure peak oxygen consumption (VO_2 peak) [17]. The initial speed of the treadmill was set to 1.7 mph (2.7 km/h), inclination 0%. In the second stage the inclination increased to 5%, while the speed of the treadmill remained at 1.7 mph. The third stage of the modified Bruce Protocol test is equal to the first stage of the standard Bruce Protocol test (i.e., the speed of the treadmill was set to 1.7 mph; inclination 10%). At each subsequent 3-minute intervals the incline of the treadmill increased by 2%.

The test was stopped if the subject could not continue due to fatigue, leg cramps, shortness of breath, chest discomfort or other medical problem. A cardiac-trained nurse (plus resuscitation equipment) was present throughout the test.

2.11. Body composition

All the body composition parameters were measured three times and an average was calculated. The skinfolds were assessed at 3 sites; abdominal, thigh, and supra-iliac (Lafayette Instrument Skinfold Calliper, model 01128) to nearest 0.2 mm [18], and the Jackson and Pollock's equation was used to estimate average percent body fat [19]. The height without shoes was measured using a portable stadiometer to the nearest millimeter and body mass was measured by a calibrated digital scale to the nearest 0.1 kg, and BMI was calculated (kg/m^2). The average waist circumference (WC) was measured at the midpoint between the iliac crest and the lower rib margin and recorded to the nearest mm [20]. All above measurements were measured at baseline and 10 weeks.

2.12. Statistical analyses

An all available data analytic strategy was chosen, regardless of intervention adherence level. The Kolmogorov-Smirnov test was used to check that all data were normally distributed before conducting parametric tests. Descriptive data included means, standard deviations (SDs) and percent distributions. Comparison of baseline variables between groups was performed using a one-way ANOVA or chi square test as appropriate for categorical variables. Repeated measures ANOVA models were used to determine Time effect and Group × Time interactions for all primary and secondary outcomes with all 3 groups in the models. Next, potential confounders were identified as variables that were statistically different between groups at baseline and related to the dependent variable of interest according to the literature or the baseline measures in this cohort, and these were entered as covariates into

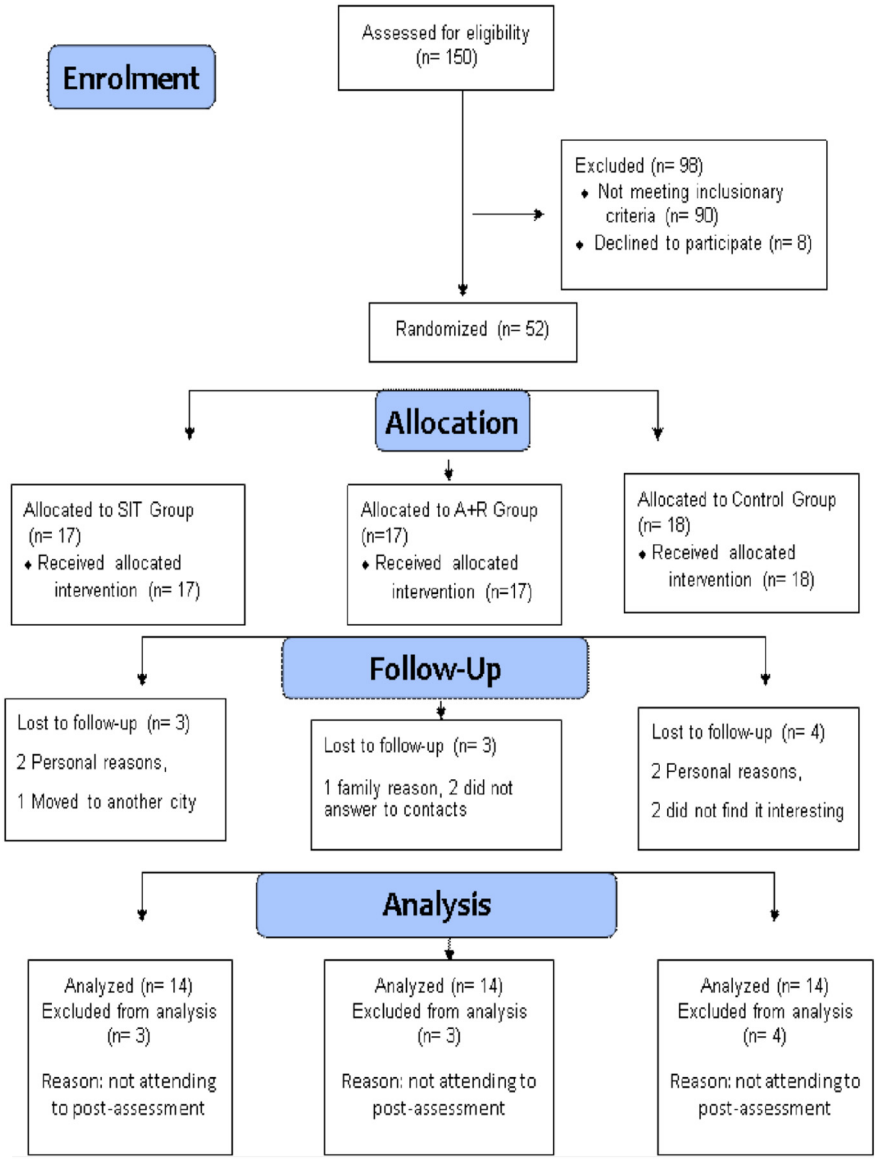

Fig. 1. CONSORT flow diagram.

repeated measures ANCOVA models as appropriate. Tukey's post-hoc *t*-tests were used to identify differences between groups when a significant difference was observed in ANCOVA models. Relationships between variables of interest were described using simple and multiple linear regression models. Statistical significance was accepted when $p < 0.05$. The SPSS statistics version 22 was used for analyses. Effect sizes of each intervention group vs. control were calculated using G Power* 3.1.2 (Kiel, Germany) [21] as: intervention group mean change − control group mean change / pooled baseline SD.

3. Results

Participant flow through the study can be found in the CONSORT flowchart in Fig. 1. Among 150 patients screened, 54 met the inclusion criteria. The main reasons for exclusion were BMI < 25, age > 60 yrs., having uncontrolled high blood pressure, severe cardiovascular diseases or cancer. Participants were randomly assigned to the SIT group ($n = 17$), A + R group (n = 17) or control group ($n = 18$). Twenty-seven participants were treated with oral hypo glycaemic medications, 20 with insulin, and 5 with combinations of insulin and oral hypo glycaemic medications. At baseline, no differences were observed between groups except for ANGPLT4 ($p = 0.041$) which was lower in control group (mean = 16.54 ± 2.95 ng/ml) than SIT and A + R groups (mean = 20.30 ± 5.33 and 19.15 ± 2.84 ng/ml), respectively (Table 2). A Tukey post hoc *t*-test showed a significant difference between SIT and control groups ($p = 0.037$).

3.1. Dropout and adherence

Data from 10 participants who did not attend the post-test assessment were excluded. The main reasons given for dropout were personal/family problems, disinterest, and moving away. Thus, all available data of 42 participants (drop out 19.2%) with mean age 55.07 ± 5.92 who completed the both assessments were analyzed. Dropouts were similar to non-dropouts in terms of age, BMI, HbA1c and level of myokines (data not shown). The adherence to training sessions was 78% in SIT and 82% in A + R groups. No significant adverse events were reported by investigators who were not blinded to group assignment during the 10-week intervention. However, most patients reported muscle soreness in their legs during SIT (76%) and A + R training (82%) in the first three sessions of training. No adverse events were reported from the control group.

Table 2
Baseline characteristics.

Characteristic	SIT (n = 14)	A + R Training (n = 14)	Control (n = 14)	p-Value
Age (years)	55.36 ± 5.94	54.14 ± 5.43	55.71 ± 6.40	0.76
Height (cm)	162.21 ± 8.02	159.21 ± 4.49	159.14 ± 5.20	0.32
Weight (kg)	77.35 ± 11.99	72.59 ± 11.48	76.30 ± 9.59	0.49
BMI (kg/m^2)	29.27 ± 3.00	28.68 ± 4.34	30.12 ± 3.52	0.58
LBM (kg)	46.14 ± 8.40	49.14 ± 16.20	42.36 ± 5.18	0.27
Body fat (%)	41.14 ± 4.34	42.57 ± 2.17	42.64 ± 4.95	0.54
WC (cm)	102.21 ± 10.68	102.14 ± 8.97	97.43 ± 11.83	0.40
SBP (mm Hg)	133.57 ± 18.65	131.43 ± 16.57	127.14 ± 23.10	0.69
DBP (mm Hg)	77.86 ± 8.93	77.14 ± 12.04	74.29 ± 12.22	0.67
$VO_{2\ peak}$ (ml/kg/min)	33.23 ± 5.98	34.37 ± 5.38	31.06 ± 5.34	0.29
FBG (mg/dl)	210.07 ± 32.91	214.64 ± 27.67	200.86 ± 46.88	0.60
Insulin (μU/ml)	10.08 ± 5.43	10.37 ± 5.36	9.55 ± 4.05	0.91
HbA1c % (mmol/mol)	9.6 ± 1.1 (82)	9.5 ± 0.9 (80)	9.0 ± 0.5 (75)	0.23
HOMA-IR	1.63 ± 0.81	1.13 ± 0.28	1.39 ± 0.63	0.37
Irisin (ng/ml)	322.14 ± 97.84	290.00 ± 99.07	262.14 ± 96.97	0.28
IL-15 (pg/ml)	3.94 ± 0.23	3.81 ± 0.23	3.86 ± 0.25	0.39
ANGPTL4 (ng/ml)	19.55 ± 3.59	19.15 ± 2.84	16.69 ± 2.72	0.04[a]
FGF21 (ng/l)	170.11 ± 71.02	176.31 ± 94.22	243.61 ± 106.77	0.08
SPARC (ng/ml)	161.44 ± 27.51	153.01 ± 25.29	138.41 ± 20.50	0.06
IL-6 (pg/ml)	1.89 ± 0.95	2.03 ± 1.08	2.12 ± 1.24	0.55

Data are presented as mean ± SD; Twenty participants who used insulin were excluded from HOMA-IR analyses.
SIT: Short sprint interval training; A + R training: aerobic and resistance training; BMI: body mass index; LBM: lean body mass; WC: waist circumference; WHR: circumference waist to hip ratio; SBP: systolic blood pressure; DBP: diastolic blood pressure; FBG: fasting blood glucose; FGF-21: Fibroblast Growth Factor 21; IL-15: Interleukine-15; SPARC: secreted protein acidic and rich in cysteine; ANGPTL4: angiopoietin-like 4; IL-6: Interleukine-6.
[a] Significant difference between SIT and control.

3.2. Serum myokine levels

Serum myokine levels are shown in Table 3. Contrary to our hypotheses, there were no significant Group × Time effects for any serum myokines. However, IL-15 was significantly reduced after training, irrespective of group assignment. The ANCOVA models did not alter the results of the unadjusted ANOVA models with respect to any Time or Group x Time effects (data not shown).

There were no significant relationships between change in any myokine and change in metabolic and body composition variables (data not shown).

3.3. Metabolic profile

As hypothesized, FBG and HbA1c levels decreased significantly in the SIT and A + R groups compared to control (See Table 4). There were positive significant relationships between baseline ANGPLT4 (r = 0.507, p = 0.0001), SPARC (r = 0.306, p = 0.04) and HbA1c. However, there were not any significant relationships between change in IL-15 (r = 0.21, p = 0.18), irisin (r = 0.27, p = 0.07), FGF21

Table 3
Primary outcomes: myokine levels.

	SIT group	A + R group	Control group	Time p value	Group × Time p value
Irisin (ng/ml)				0.09	0.69
Pre	322.14 ± 97.84	290.00 ± 99.07	262.14 ± 96.97		
Post	364.29 ± 170.69	358.57 ± 142.12	279.29 ± 108.73		
Mean difference	42.15	68.57	17.15		
IL-15 (pg/ml)				0.02*	0.57
Pre	3.94 ± 0.23	3.81 ± 0.23	3.83 ± 0.29		
Post	3.71 ± 0.38	3.60 ± 0.25	3.76 ± 0.29		
Mean difference	-0.23	-0.21	-0.07		
ANGPTL4 (ng/ml)				0.31	0.30
Pre	19.55 ± 3.59	19.15 ± 2.84	16.69 ± 2.72		
Post	18.89 ± 3.27	19.99 ± 3.54	18.53 ± 3.21		
Mean difference	−0.66	0.84	1.84		
FGF21 (ng/l)				0.26	0.50
Pre	170.11 ± 71.02	176.31 ± 94.22	243.61 ± 106.77		
Post	229.63 ± 94.89	204.67 ± 111.36	235.96 ± 69.74		
Mean difference	59.52	28.36	−7.65		
SPARC (ng/ml)				0.72	0.14
Pre	161.44 ± 27.51	153.01 ± 25.28	138.41 ± 20.50		
Post	146.55 ± 25.22	150.39 ± 19.09	150.16 ± 26.03		
Mean difference	-14.89	-2.62	11.75		
IL-6 (ng/ml)				0.002*	0.009[a]
Pre	1.89 ± 0.95	2.03 ± 1.08	2.12 ± 1.24		
Post	1.21 ± 1.11	1.50 ± 1.32	1.88 ± 2.01		
Mean difference	-0.67	-0.52	-0.23		

Data are presented as mean ± SD; FGF-21: Fibroblast Growth Factor 21; IL-15: Interleukine-15; SPARC: secreted protein acidic and rich in cysteine; ANGPTL4: angiopoietin-like 4; IL-6: Interleukine-6.
* Significant differences within groups.
[a] Significant differences between groups.

Table 4
Secondary outcomes.

	SIT group	A + R group	Control group	P between groups	P Time × Group
Weight (kg)				0.02*	0.48
Pre	77.35 ± 11.99	72.59 ± 11.48	76.30 ± 9.59		
Post	77.01 ± 12.35	72.34 ± 11.39	75.55 ± 9.23		
Mean difference	−0.34	−0.25	−0.75		
BMI (kg/m$^{2)}$				0.01*	0.43
Pre	29.27 ± 3.00	28.68 ± 4.34	30.12 ± 3.52		
Post	29.14 ± 3.12	28.59 ± 4.35	29.82 ± 3.37		
Mean difference	−0.13	−0.09	−0.3		
LBM (kg)					
Pre	46.14 ± 8.40	49.14 ± 16.20	42.36 ± 5.18	0.01*	0.38
Post	42.64 ± 2.24	42.36 ± 4.31	40.64 ± 5.24		
Mean difference	−3.5	−6.78	−1.72		
BF%				0.32	0.20
Pre	41.14 ± 4.34	42.57 ± 2.17	42.64 ± 4.95		
Post	42.64 ± 2.24	41.43 ± 4.18	44.50 ± 2.17		
Mean difference	1.5	−1.14	1.86		
$VO_{2\ peak}$ (ml/kg/min)				0.0001*	0.02[a]
Pre	33.23 ± 5.98	34.37 ± 5.38	31.06 ± 5.34		
Post	40.67 ± 4.90	38.09 ± 6.03	33.13 ± 6.82		
Mean difference	7.44	3.72	2.07		
FPG (mg/dl)				0.0001*	0.03[a]
Pre	210.07 ± 32.90	214.64 ± 27.67	200.86 ± 46.88		
Post	137.36 ± 32.95	163.86 ± 71.47	190.50 ± 59.71		
Mean difference	−72.71	−50.78	−10.36		
Insulin (μU/ml)				0.02*	0.47
Pre	10.08 ± 5.43	10.37 ± 5.35	9.55 ± 4.05		
Post	8.18 ± 5.75	8.83 ± 7.60	9.16 ± 3.75		
Mean difference	−1.9	−1.54	−0.39		
HbA1c (%)				0.0001*	0.006[a]
Pre	9.64 ± 1.08	9.49 ± 0.86	9.10 ± 0.51		
Post	7.82 ± 0.93	8.25 ± 1.22	9.12 ± 1.41		
Mean difference	−1.82	−1.24	0.02		
HOMA-IR				0.007*	0.02[a]
Pre	1.63 ± 0.83	1.13 ± 0.28	1.39 ± 0.63		
Post	1.15 ± 0.74	0.95 ± 0.24	1.42 ± 0.71		
Mean difference	0.21	1.38	1.12		

Data are presented as mean ± SD; Twenty participants who used insulin were excluded from HOMA-IR analyses; SIT: Short sprint interval training; A + R training: aerobic and resistance training; BMI: body mass index; BF%: body fat percent; LBM: lean body mass; FBG: fasting blood glucose.

* Significant differences within groups.

[a] Significant differences between groups

($r = -0.17$, 0.27), ANGPLT4 ($r = 0.08$, $p = 0.58$), SPARC ($r = 0.20$, $p = 0.19$) and HbA1c. After running liner regression for each group separately there were still no significant relationships between IL-15 ($r = 0.50$, $p = 0.07$), FGF21 (−0.15, $p = 0.60$), ANGPLT4 (0.05, $p = 0.85$), SPARC ($r = -0.02$, $p = 0.94$) and HbA1c in A + R group. Similar, no significant relationships between myokines and HbA1c in SIT group [irisin (r = 0.50, p = 0.07), SPARC ($r = 0.51$, $p = 0.06$), FGF21 and HbA1c (−0.11, $p = 0.70$)] and control group [IL-15 ($r = 0.07$, $p = 0.78$), irisin (0.17, $p = 0.54$), FGF21 (−0.11, $p = 0.68$), SPARC (−0.06, $p = 0.82$), ANGPLT4 ($r = -0.18$, $p = 0.50$) and HbA1c].

3.4. Aerobic capacity

Aerobic capacity increased significantly in both A + R and in SIT compared to the control group (see Table 4). These changes represented an average 27.31% increase in $VO_{2\ peak}$ in the SIT and 10.82% in the A + R exercise groups. There was a positive significant association between changes in ANGPTL4 ($r = 0.61$, $p = 0.02$), IL-15($r = 0.70$, $p = 0.006$) and changes in VO2 $_{peak}$ in SIT group, but no relationships with the other myokines.

However, there were no significant relationships between changes in any of myokines FGF21 ($r = -0.45$, $p = 0.10$), ANGPTL4 ($r = -0.21$, $p = 0.48$), IL-15 ($r = 0.14$, $p = 0.64$), irisin ($r = -0.34$, $p = 0.23$), SPARC ($r = -0.27$, $p = 0.35$) and change VO2 $_{peak}$ in the A + R group or control group (data not shown for control group).

3.5. Body composition

Body composition changes are shown in Table 4. Weight, lean body mass (LBM) ($p = 0.01$) and BMI (p = 0.01) all decreased significantly over time, irrespective of group assignment. There was no significant relationship between changes in any myokines and body compositions in SIT, A + R and control groups (data not shown).

4. Discussion

Contrary to our hypotheses, neither modality of exercise affected chronic levels of myokines in this cohort. The significant myokine changes were decreases in IL-15 and IL-6 after 10 weeks, irrespective of group allocation. However, it was notable that the change in this myokine and ANGPTL4 were directly associated with the change in aerobic capacity in the SIT group, the group with the most robust changes in fitness. It is possible therefore, that even greater fitness adaptations than those observed in the SIT group would be required to demonstrate a significant change in these myokines after training. In addition, $VO_{2\ peak}$ remain increased 48 h after chronic A + R and SIT trainings compared to control group in overweight women with type 2 diabetes. Furthermore, metabolic outcomes such as HbA1c and FBG still decreased by Group × Time at 48 h after the trainings. Furthermore, there were significant change in weight, LBM, BMI and insulin over time in all groups.

There have been a few studies on effect of SIT and combined training (resistance and endurance) on cytokines peptides and

metabolic outcomes in women with type 2 diabetes [27–31]. However, to the best of our knowledge, this is the first study to evaluate the effect of sprint interval (SIT) and combined aerobic and resistance trainings (A + R) on serum myokines and metabolic outcomes in overweight women with type 2 diabetes.

Contradictory results have been reported in changes to serum IL-15. A previous study revealed the level of serum IL-15 is higher in diabetes compared to healthy individuals [22,23]. Our study investigated that there was a reduction in serum IL-15 over time in all groups, however, the reduction was higher in the experimental groups compared to the control group in overweight women with type 2 diabetes at 48 h after chronic trainings. Riechman et al. [24] demonstrated a significant increase ($p < 0.05$) in plasma IL-15 protein levels immediately following whole-body resistance exercise (80% of one repetition maximum, performing three sets (6–10 repetitions) of 13 resistance exercises, 3 days a week) on young healthy individuals (mean age 20.9 ± 2.5 yrs). However, there was no effect from 10 weeks training on the post-exercise release of IL-15 in the study [24]. In contrast, a similar study in untrained healthy young males reported no increase in plasma IL-15 levels at intervals from 6 to 48 h following an intensive resistance exercise protocol which involved only the quadriceps muscles. However, increases in quadriceps muscle IL-15 mRNA expression were observed 24 h after exercise [10].

Ostrowski et al. [25] observed no changes in plasma IL-15 following 2 h of treadmill running with 75% of maximal oxygen consumption (VO2 max) in male athletes. Similarly, Andersson et al. [26] found no acute effect of competition on IL-15 levels in elite soccer females. In contrast, a study on sedentary postmenopausal women (mean age 63.18 ± 4.8 yrs.; body mass 57.84 ± 7.70 kg) Prestes et al. [27] reported an increase in plasma IL-15 levels 48 h following the first session of resistance training but no effect following 16 weeks of training (three sets of 6–14 maximum repetition, twice per week). Discrepancies between these studies may be due to the differences in the intervals between modalities of exercise, times between last session of training and drawing blood samples and cohorts.

Contrary to our hypotheses, we observed no significant changes in FGF21 after either resistance or aerobic training compared to control. Interestingly, previous studies have reported divergent results in the serum level of FGF21. A current study reported that there is an increase in FGF21 level after a two-week aerobic training (following the Bruce's protocol, 85% of the maximum predicted heart rate). The mean duration of the exercise tests was 14.2 ± 1.4 min/session and a majority of participants reached stage four of the Bruce protocol, with a mean METs consumption of 12.2 ± 2.4. In sedentary young healthy women (mean age 24.0 ± 3.7 yrs and mean BMI 21.4 ± 7.0 kg/m^2), however, acute exercise did not change the serum levels FGF21 [8]. Conversely, 3 months of combined aerobic and resistance training composed of 45 min of aerobic exercise at an intensity of 60–75% of the age-predicted maximum heart rate (300 kcal/session) and 20 min of resistance training (100 kcal/session) five times a week decreased the serum level of FGF21 in non-diabetes obese women (mean age 45.3 ± 9.5 yrs., mean BMI 27·6 ± 2·4 kg/m^2) [7]. However; another study with 2 months of 45–60 min exercise sessions consisting mainly of cycling and running at a target heart rate corresponding to 35–85% of their VO2 max, five times a week did not change the circulating FGF21 in non-diabetes obese men (mean age 35.4 ± 1.5 yrs) [5]. Another study with an acute bout of endurance exercise (a treadmill running for 30 min at 50 or 80% VO2 max in a climate chamber between 2 and 5 p.m., environmental conditions maintained at 24.5 ± 0.3 °C, 50 ± 3.0% relative humidity, and 1 m/s air velocity) serum FGF21 level was significantly higher than that before acute exercise, while there was no difference in serum FGF21 level between before and immediately after acute exercise. In addition, after the 1 h recovery from high-intensity exercise (80% VO2 max), serum FGF21 level was higher than that after the 1 h recovery from mild intensity exercise (50% VO2 max) in young healthy men (mean age 20.1 ± 0.3) cohorts [28]. As previous studies have shown, FGF21 is a metabolic regulator which exerts anti-diabetes and lipid-lowering effects in type 2 diabetes [39–41]. We found a positive significant correlation between ANGPLT4, IL-15 level and VO2 peak in SIT group. There is a small literature on myokines and cardiovascular fitness which does not include any of the myokines measured in our study. This is the first study to measure the relationship between these myokines and VO2 peak Duzova et al. reported a negative correlation with IL6 (which was not measured in our study) and VO2 max ($p < 0{,}021$, $-0{,}591$) which is completely opposite to our result. We found that there was a positive moderately significant relationship between ANGPLT4, SPARC and HbA1c at baseline which was no longer significant in change. There is a small literature on the relationship between these myokines and HbA1c. Results reported by Kotani et al. after a 6-month weight reduction intervention based on lifestyle modification including diet (restricting the total energy intake according to the individual's ideal weight, with balanced nutrient content as determined by a professional dietician) and exercise (≥ 30 min at a moderate intensity at least 3 days per week as recommended by an exercise instructor) on obese men (mean age 46.7 ± 6.9 yrs) [29] indicated changes in SPARC levels were significantly and positively correlated with HbA1c ($p < 0.05$). Apparently, the correlation between SPARC and the chronic glycaemic marker HbA1c in our baseline data appears to be in line with previous data showing high circulating SPARC levels in patients with diabetes [30,31].

Contrary to our hypotheses, we observed no significant changes in irisin after either resistance or aerobic training compared to control. Both trials were conducted at the same time of day with intervals of > 1 week. Blood samples were collected before exercise, immediately after exercise and at 3, 6 and 19 h after exercise. Serum irisin concentrations were significantly higher in low intensity than high intensity ($p < 0.05$). Although the irisin concentration did not change significantly after high intensity, a significant reduction was observed immediately after low intensity ($p < 0.05$). Serum irisin concentrations 3 and 6 h after exercise were significantly lower in high intensity than in low intensity ($p < 0.05$). Relative irisin concentrations immediately after exercise and at 6 and 19 h after exercise ($p < 0.05$) were significantly higher in high intensity than in low intensity. Therefore, we speculated that high intensity exercise would cause greater irisin response than low intensity exercise [32]. The difference may be due to our cohort selection (older women with type 2 diabetes) or the timing of our blood draw (48 h post final exercise session), as acute elevations could have dissipated. Huh et al. (2012) reported that a single bout of sprint interval exercise composed of 2 or 3 sets of two 80-m sprint runs in each set with 20 min rest between sets on young, moderately trained, healthy males (age 20.5 ± 1.5 years, BMI 21.9 ± 1.6 kg/m2) significantly increased irisin concentration (18% higher than pre-exercise values) but did not change after a chronic eight-week program. The study indicated that muscle mass is the main predictor of circulating irisin levels in humans [33]. Similar to our result, a study with resistance group (eight exercises with set of three or four of 12 repetitions, with 65% of 1RM with 2 min rest between sets), endurance training group (60 min of pedalling at 65% of VO2 max at 60 rpm) and combined resistance and combined group (30 min of four resistance exercises; chest press, lat-pull down, leg press, and shoulder press followed by a 20-min rest and then 30 min of endurance exercise at 65% of VO2 max) observed the endurance and combined endurance and resistance trials did not show significant changes in plasma irisin concentrations during the 6 h after the exercises. In contrast, the resistance trial showed a significant increase in plasma irisin concentration 1 h after exercise ($P < 0.05$). Furthermore, the plasma irisin concentration 1 h after exercise was significantly higher in the resistance than endurance and combined trials ($P < 0.05$) [34].

In our study, there was no statistically significant change in SPARC level between groups. A previous study [35] indicated that SPARC levels were higher in subjects with type 2 diabetes compared with

impaired glucose regulation and healthy subjects (16.74 ± 6.99 vs 14.04 ± 8.03 μg/l, P < 0.05 and 16.74 ± 6.99 vs 11.72 ± 4.47 μg/l, $P < 0.01$ respectively). Aoi and et al. (2012) [36] indicated that serum SPARC was transiently increased immediately after a single bout of cycling at 70% VO2 max for 30 min in young healthy men (Blood samples were collected at 0, 3, 6, and 24 h later).

We did not find any significant change in ANGPTL4 serum between the groups. A study on inactive men (40–65 years) who were divided into a control group with normal weight (23.5 ± 2.0 kg/m^2) and normal fasting and 2-hour serum glucose levels and a hyperglycaemic group (29.0 ± 2.4 kg/m^2), with a combined strength (whole-body strength training) and endurance training (bicycle sessions with 50–60% VO2 max) program for 12 weeks, plus a carbohydrate-rich meal on average 2475 KJ which was provided 90–120 min before the exercise test showed no change in ANGPTL4 serum immediately after acute exercise in either group (control or hyperglycaemic) at baseline, but was slightly increased acutely at 12 weeks in the control. Two hours post-exercise ANGPTL4 levels increased approximately two- and three-fold as compared to before acute exercise in control and hyperglycaemic individuals, respectively. The absolute serum levels of ANGPTL4 were significantly higher in the hyperglycaemic group compared to the control 2 h post exercise at baseline as well as after 12 weeks of training, and the relative increase from before acute exercise to after 2 h rest was significantly higher in the hyperglycaemic individuals than the control after 12 weeks of training ($P = 0.03$) [37].

Based on these analyses, both exercise training regimes did not have significant effects on some adipo-myokines, except with Il-6. The dissociation in patterns of exercise-induced changes in serum concentration of these myokines might be due to the fact that circulating IL-6 increased robustly, whereas other myokines such as FGF21, ANGPTL4 and IL-15, increased modestly in response to muscle contraction in diabetes type 2 patients [38]. Furthermore, other tissues may contribute more than skeletal muscle to the exercise-induced changes in circulating levels of these adipo-myokines [38]. It seems that unchanged serum myokine concentration after 10-weeks chronic exercises and discrepancy in reports could be due to the difference in metabolic states, critically important timing of measurement [5], the discrepancy of applied exercise intensities [39] and variations in analytical and pre-analytical conditions (sample collection method, data collection, calculation and others, all of which might lead to inaccuracy to myokine quantification) [40].

Previous studies have shown that combined A + R training compared to either aerobic or resistance training alone or control group significantly reduced metabolic profiles in type 2 diabetes [50–52]. Similar results seem to be consistent with high intensity training which improved glycaemic control in individual with obesity or type 2 diabetes [53–55]. These results support our study which showed SIT and A + R trainings reduced HbA1c and fasting blood glucose in overweight women with type 2 diabetes.

5. Conclusions

Taken together, the results of the present study showed no significant differences in serum myokines between groups after 48 h of chronic SIT and combined aerobic and resistance training in overweight women with type 2 diabetes.

However, for many of the myokines identified to date, the information available is limited and not enough to characterize precise functions and activities in exercise programs in humans. Further research needs to be done, drawing blood at different times after the final session of training in the various exercise modalities.

Ethics approval and consent to participate

Ethical committee of Shahrekord University (Code No: SKU94/210) granted ethical approval for the study.

Consent for publication

Not applicable.

Availability of data and material

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Ebrahim Banitalebi, AbdolReza Kazemi, Mohammad Faramarzi, SamiraNasiri, Marjan Mosalman Haghighi designed the study. S. Nasiri and E. Baitalebi supervised exercise training protocols. Ebrahim Banitalebi, AbdolReza Kazemi, Mohammad Faramarzi, SamiraNasiri supervised laboratory exams and data collection. Ebrahim Banitalebi and Marjan Mosalman Haghighi analyzed and interpreted the data. Ebrahim Banitalebi and Marjan Mosalman Haghighi wrote the first draft of the manuscript. Mohammad Faramarzi edited the paper. All authors contributed to the writing of the paper. All authors read and approved the final manuscript.

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Availability of data and materials

All data generated or analyzed during present study are included in this paper.

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