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RESEARCH ARTICLE

# *Chlorella vulgaris* in combination with high intensity interval training in overweight and obese women: a randomized double-blind clinical trial

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**Background** *Chlorella vulgaris* (CV) as a multifunctional dietary supplement is known with lots of health benefits. It is possible that CV consumption along with high-intensity interval training (HIIT), a short period exercise is more beneficial. This investigation aimed to evaluate the effects of CV and/or HIIT on anthropometric parameters and cardiometabolic risk factors among overweight or obese women.

**Methods** Present randomized double-blind clinical trial, included 46 women with overweight or obesity and randomly assigned them to four groups including CV, HIIT, CV+HIIT, and placebo. CV supplementation was 900 mg a day and HIIT program 3 sessions a week. Dietary intake, anthropometric assays and blood samples were taken at the commencement and completion of 8-week intervention.

**Results** After 8 weeks, waist circumference (WC) significantly reduced in CV+HIIT group in comparison with placebo group. Significant decreases in triglycerides (TG) and low-density lipoprotein (LDL) cholesterol levels were found after CV supplementation and/or HIIT exercise in comparison with placebo group. A significant rise in high-density lipoprotein (HDL) cholesterol level was observed in HIIT and HIIT + CV groups in comparison with placebo group, however CV consumption failed to affect HDL cholesterol levels. CV and/or HIIT significantly lowered, visceral adiposity index (VAI), lipid accumulating product (LAP) and atherogenic index of plasma (AIP) in comparison with placebo. However, concurrent administration of CV and HII resulted in greater reduction in this indexes. Among glycemic indices a significant reduction in insulin resistance in CV+HIIT group compared with placebo group were seen.

**Conclusions** In conclusion, CV and HIIT could improve lipid profile and glycemic status in overweight and obese women.

**Keywords** Obesity · High Intensity Interval Training (HIIT) · *Chlorella vulgaris* (CV)

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## Introduction

Obesity is a chief health concern worldwide, with high prevalence; it often results in some diseases such as cardiovascular problems, diabetes and cancer. [1]. Based on recent investigations, probably, of the four most noticeable risk factors, obesity is the most important one, according to some criteria, with a high health priority [2]. In comparison with 1980, the obesity prevalence has been intensified in many countries, resulting in 120 million disability adjusted life years (DALYs) that could be attributed to overweight and obesity [3]. According to the results of a systematic review, based on articles from 2005 to 2014, overweight and obesity prevalence among Iranian adults population was between 12.8-76.4 and 2.4-35.4 %, respectively [4]. Concurrently,

the management of obesity is regarded a major modifiable intervention to prevent chronic diseases. [5]. Immobility is defined as one of the main hazardous factors in obesity development [6]. However, there is consensus that following physical activity for a period of at least 150 minutes per week with moderate intensity, or 60-75 minutes per week with vigorous intensity can be effective in maintaining the overall health; however, more than 31% of adults fail to reach the suggested minimum levels of physical activity [7]. Many studies have shown that exercise is an effective approach to tackle weight reduction and improve the health consequences of obesity treatment, as energy restriction alone leads to considerable reductions in the fat-free mass (FFM) and energy expenditure, as well as metabolic disorders; these all make it difficult to lose more weight and maintain the reduced weight [8]. Accordingly, following a regular physical activity program should be an important part of each weight management program. In this regard, resistance, endurance, and high-intensity interval exercises are effective choices [9]. However, a high volume of exercise might be a major obstacle limiting physical activity/exercise because time deficiency is a commonly mentioned factor accounting for poor adherence to exercise programs [10]. However, physical activity and calorie restriction are common strategies for weight loss [11]. Recently, high-intensity interval training (HIIT), because of its short time, has been suggested as a component of weight management programs [12]. Replacement of usual exercise programs with HIIT, as a time-saving exercise, makes it more practical to continue physical activity as a routine [13]. Moreover, increasing evidence demonstrates the beneficial effects of HIIT on hyperlipidemia, hyperglycemia and anthropometric parameters [14].

Besides lifestyle modifications, dietary supplements are helpful choices; among them, microalgae have received extensive scientific attention due to their great bioactive constituents. *Chlorella vulgaris* (CV), a type of single cellular fresh water green algae, is more popular worldwide, particularly in Eastern countries. CV contains essential nutrients including fiber, vitamins, minerals, essential amino acids and phytochemicals, making it an appropriate functional food [15]. Data extracted from animal studies have revealed the valuable effects of CV on obesity [16–20], dyslipidemia [21] and glucose status [22]. Some clinical trials have also investigated the therapeutic effects of CV, reporting its valuable effects on disorders related to obesity; these comprise insulin resistance, dyslipidemia, inflammation and further cardiovascular consequences [23–25]. One study on an animal model showed the synergistic effect of CV and exercise on the metabolic disorder [26]; meanwhile, to the best of our knowledge, there has been no clinical trial regarding the combined effect of CV and HIIT.

We hypothesized that CV or HIIT would be effective in improving obesity-related metabolic abnormalities, and the combination of treatments would provide more beneficial effects than each of CV or HIIT alone. Thus, this study was designed to find the possible effects of CV and/or HIIT on anthropometric parameters, glycemic status, and lipid profile among overweight and obese women.

## Materials and methods

### Subjects

Present study which was designed as a randomized, double-blind, placebo-controlled trial was performed in Tabriz city in Iran, between June 2019 to November 2019. In the present study, principles of the ethics committee of Tabriz University of Medical Sciences (IR.TBZMED.REC.1397.922) was followed and this institute confirmed the study procedure. In addition, participants were aware of purposes and study protocol. Finally they signed informed consents for their inclusion. This clinical trial was registered at the Iranian Registry of Clinical Trials (www.irct.ir) with the number IRCT20190224042821N1. Flow diagram 1 represents participant's summary (Fig. 1).

### Study design

Any obese or overweight woman aged 18–35 years with body mass index (BMI), ranged between 25 to 35 kg/m$^2$ could be entered in the study in absence of exclusion criteria. Main exclusion criteria were continuous physical activity, pregnancy or lactation, impaired glucose status, hepatic, renal or cardiovascular disorders, and joint disabilities. . In addition to antioxidant supplements, taking any kind of multivitamin, minerals, anti-inflammatory supplements, and non-routine supplements was one of the exclusion criteria. Following a restricted diet (vegan, calorie restriction or any of conventional dietary programs) and/or a specific physical exercise and using any kind of tobaccos or alcoholic drinks were not included as well.

This study was a 8-wk randomized, double-blind, placebo-controlled trial involving 4 treatment groups: CV, HIIT+placebo, CV+HIIT, and placebo. Groups CV+HIIT and HIIT+placebo received three capsules of CV or placebo daily in combination with three sessions/week of HIIT. Groups CV and placebo just received three capsules of CV or placebo daily for 8 weeks. Randomization for individual assignment in each group was done using the computer-generated random numbers by a statistician. Considering $\alpha = 0.05$, 95% confidence, and power of 80%, the sample size was calculated 9 subjects in each group

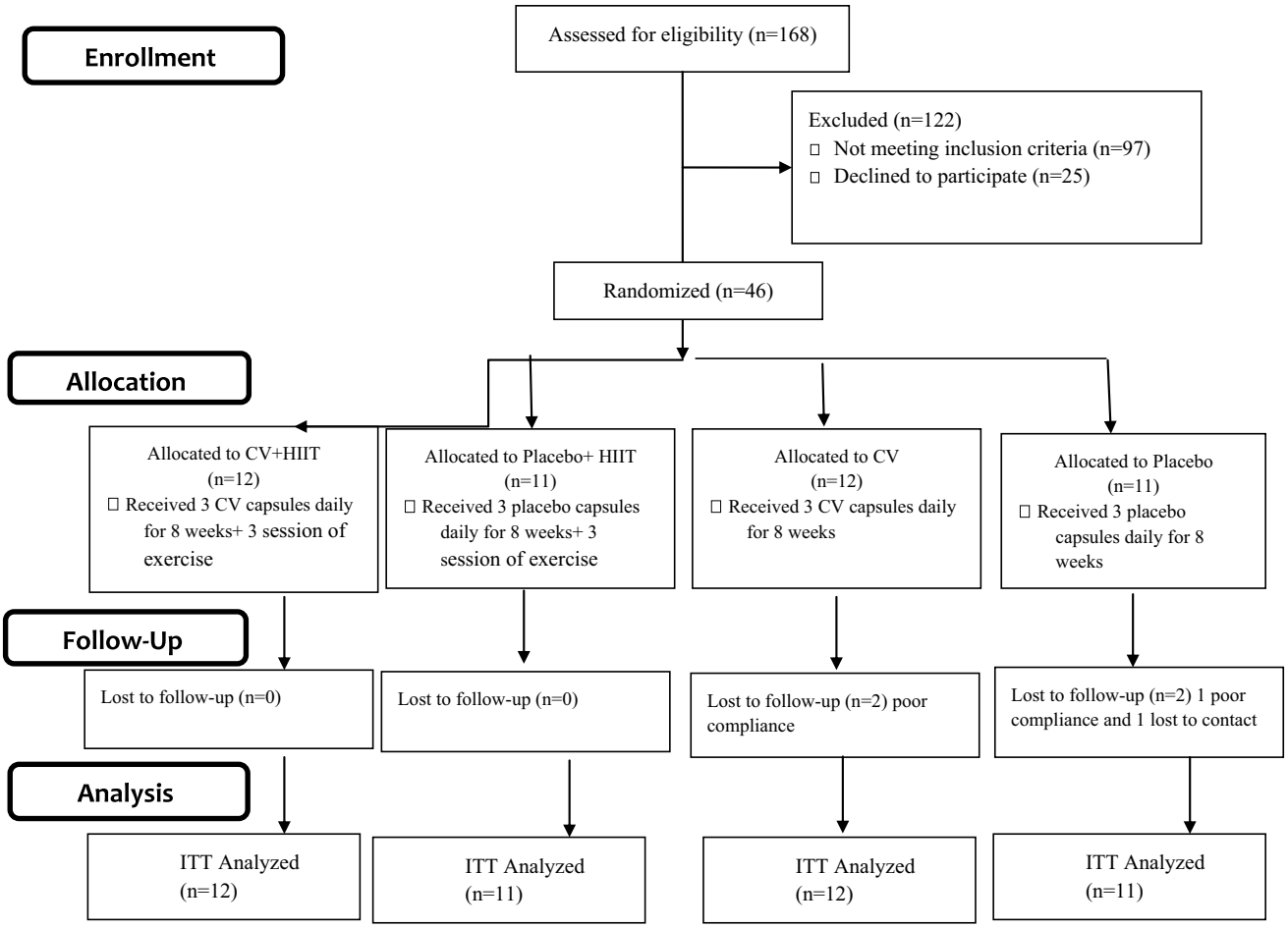


**Fig. 1** Flow diagram of study participants

based on fasting blood sugar (as secondary outcome) extracted from previous investigations [23]. By anticipating a 20% drop-out rate, we included 12 and 11 participants in every two arms and a total 46 via this formula:

$$n = \frac{(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta})^2 (S_1{}^2 + S_2{}^2)}{(X_1 - X_2)^2}$$

Group 1 and 2 received three capsules of CV and placebo daily combined with three sessions of high-intensity interval training (exercise protocol is presented in the appendix). Groups 3 and 4 only received three capsules of CV and a placebo daily for 8 weeks. The intervention assignment was blinded for the investigators and participants. Pure CV powder was supplied from a knowledge-based company (Riz Jolbaki Parsian, Rasht, Guilan, Iran) and put in dark capsules weighing 300 mg (because pharmacological benefits were seen in similar doses) in a pharmacological laboratory under a sterile condition (Baharan pharmacology company, Tabriz, Iran). CV and placebo capsules were identical to each other in terms of color and size, but placebos were filled with corn starch. Both CV and placebo were divided into 90 capsules in identical jars with the same label. During the intervention period, the dietitian visited participants at the baseline and once every two weeks; this was done till the end of intervention to evaluate the compliance of the participants to the study protocol and to ask them about possible adverse effects. In these intervals, volunteers were asked to preserve their jars to receive the new one, and the remaining capsules were counted. The participants with the compliance of less than 90 percent were assumed to be omitted.

## Anthropometric measurements

The anthropometric parameters were assessed at the beginning and after the 8-week intervention completion. Height measurement was done via a wall mounted Stadiometer (Seca, Hamburg, Germany) with 0.1 centimeter accuracy. Body weight was measured after an overnight fasting with the least clothing using an identical scale (Seca, Hamburg,

Germany) by 0.1 kilogram accuracy. Then BMI was calculated by division of weight in kilogram to the height in meters to the power of two. Waist circumference (WC) was measured via a soft tape at the narrowest circumference between the iliac crest and the last rib, about two centimeters above the navel. Hip circumference (HC) was measured around the outstanding point of bottom and the ratio of WC to HC which is called WHR (waist to hip circumference) was calculated.

## Dietary intake and physical activity

Dietary intake was evaluated based on the dietary food record (three non-consecutive days) before and after the intervention; the subjects were requested not to change their dietary pattern. Participants were instructed to record the amount of the consumed foods and beverages in portion sizes and volumes, so the amounts could be defined correctly. Finally, the dietary food records results were analyzed using the Nutritionist IV (N4) software. In order to ensure that this recommendation would be applied, a brief food recall was taken in every visit every two weeks. However, the participants were asked to preserve their routine physical activity (no additional activity in exercise groups). To determine the basic physical activity levels of the participants as a confounding effect, the International Physical Activity Questionnaire short form (IPAQ-S) was recorded for each person, even in the exercise groups. Individual's physical activity was stated as metabolic equivalents (METs) in minutes per week. In two groups following the exercise program, the participants were persuaded to follow the sessions without any interruption; they were eliminated if they joined less than 75% of the sessions.

## HIIT protocol

Exercise program was designed according to the mean vo2max of the participants, which was assessed via the Bruce test. Total protocol consisted of 8 weeks; the first two weeks were intended to prepare the participants and the other 6 covered the main treatment period. Exercise started by 50-60% intensity of individuals and increased week by week; this was increased to 90-100% from the fifth week. The maximum heart rate for each participant was calculated based on the Karvonen formula, according to the resting heart rate and age. This program was carried out three sessions a week; it was continued for less than one hour; in a step-by-step manner, the time was reduced and intensity was increased. To pursue the exercise program, an expert trainer was present in the gym to monitor the correctness of the protocol by following and helping the participants to warm up and cool down properly. As all HIIT programs, the main protocol consisted of workout and rest periods (for further information, the protocol can be seen in the appendix).

## Laboratory assays

Fasting blood samples (8 cc) were collected following an overnight fast (10 to 12 hours) in the morning at the beginning and end of intervention. Blood samples were centrifuged with 3500 rpm speed for ten minutes for obtaining blood serums and kept in −80°C until biochemical analysis. Before freezing the samples, fasting blood sugar (FBS) and lipid profile including triglyceride (TG), total cholesterol (TC), and high-density lipoprotein (HDL) cholesterol measurements were done by enzymatic colorimetric method and commercial kits (Pars Azmun, Tehran, Iran). Friedewald equation was applied to calculate low-density lipoprotein (LDL) cholesterol in those with TG below 400 mg/dL. All tests were done at an identical laboratory using standard laboratory methods. Visceral adiposity index (VAI), lipid accumulation product (LAP) and atherogenic index of plasma (AIP) were calculated based on the measured formulas as follows:

$VAI=[WC/36.58+(1.89\times BMI)]\times(TG/0.81)\times(1.52/HDL\ cholesterol)$ [27], $LAP=[WC\ (cm)-58]\times[TG\ (mmol/l)]$[28] and $AIP=[\log(TG/HDL\ cholesterol)]$ [29].

Insulin levels were assessed with enzyme-linked immunosorbant assay (ELISA) with (Pars Azmun, Tehran, Iran) and HOMA-IR, as an insulin resistance indicator was calculated with:

HOMA-IR = [glucose (nmol/L) * insulin (μU/mL)/22.5] formula.

## Statistical analysis

Considering α=0.05, 95% confidence, and power of 80%, the sample size was calculated 9 subjects in each group based on fasting blood sugar (as secondary outcome) extracted from previous investigations [23]. By anticipating a 20% drop-out rate, we included 12 and 11 participants in every two arms and a total 46. Data analyses were performed formed on the intention-to-treat (ITT) method. Missing data were imputed based on the Last-Observation-Carried-Forward (LOCF) method. To examine the normality of variables distribution, the Kolmogorov-Smirnov test was applied. For continuous variables analysis, one-way analysis of variance (ANOVA) and for categorical variables comparison, chi-square tests were used. Analysis of covariance (ANCOVA) adjusted for baseline values, age, and mean changes in BMI were applied to evaluate the absolute effect of treatments on anthropometric and metabolic parameters.

SPSS software version 23 (Chicago, Illinois, USA) was used for statistical analyses and significance level assumed *P*-values less than 0.05.

## Results

As it is revealed in the study diagram based on Consort (Fig. 1), 42 participant accomplished the clinical trial. Two participants in the CV group [abdominal cramps ($n = 1$), poor supplement compliance ($n = 1$)] and 2 in the placebo group, [personal reasons $n = 1$, poor compliance $n = 1$] were excluded. Finally analysis was done on the ITT method, therefore all 46 participants were included in the analysis. Except for one person who complained from abdominal cramps, no other serious side effects for CV or placebo use were reported during the study.

Table 1 demonstrates the general characteristics of the study subjects in four groups. As it's shown, no significant differences in age and marital status were observed between groups, except for education levels.

As presented in Table 2, height, weight, BMI, HC, WC and WHR had no significant between-group differences at the baseline and after the end of intervention. No significant between-group changes were observed in weight, BMI, HC, and WHR based on ANOVA and ANCOVA tests, however, there was a significant between- group difference in WC after adjusting for baseline, and potential confounders. The results from Bonferroni post hoc pairwise comparisons revealed that CV+ HIIT could significantly reduce WC in comparison with other study groups (MD [CI 95%]: -3.67 (-5.23, -2.11), $p < 0.05$).

Based on the three days dietary records which were collected at baseline and end of intervention, no significant differences was observed in total energy intake, protein, carbohydrate, fat, cholesterol and dietary fiber between groups and within groups before and after the intervention (Table 3). In this table physical activity is mentioned in baseline and after the intervention calculated via IPAQ-S. As it is indicated, in baseline there is no significant difference between groups, but as it was anticipated after the intervention in two groups which has exercise significant change is seen in comparison with other two groups ($p = 0.001$ in HIIT+CV and $p < 0.001$ in HIIT+Placebo group). In CV group, there is an unwanted increase in physical activity although the recommendations ($p = 0.023$).

Baseline serum levels of lipid profile including TG, TC, LDL cholesterol and HDL cholesterol did not significantly differ between groups ($p > 0.05$) (Table 4). Serum TG significantly decreased ($p = 0.042$) was found subsequent to CV supplementation and/or HIIT. The combination of CV and HIIT was compared with the placebo group based on ANCOVA test adjusted for baseline and confounders. The changes in TC level was not significant between groups based on ANOVA or ANCOVA tests. There was a significant decrease in LDL cholesterol level in CV, HIIT+Placebo, and CV+HIIT groups ($p = 0.001$) compared with placebo group, after adjusting for baseline and confounding factors. Furthermore, CV in combination with HIIT caused a larger change in serum LDL cholesterol in comparison with other groups. Analyses based on ANOVA and ANCOVA tests showed a significant increase in serum HDL cholesterol level ($p = 0.002$) in HIIT+Placebo and HIIT + CV groups in comparison with placebo and CV groups.

AIP, LAP and VAI measures had no significant differences in the baseline. Significant between-group differences were observed in these measures after adjusting for baseline and confounders (AIP $p < 0.001$, LAP $p = 0.010$ and VAI $p < 0.001$). When Bonferroni test applied, significant reductions were observed in CV+HIIT, HIIT + Placebo, and CV in comparison with placebo.

The effects of the interventions on glycemic status are presented in Table 5. Comparison of baseline levels of FBS, insulin, and HOMA-IR indicated no significant differences between the four groups ($p > 0.05$). No significant between-group differences were observed in FBS. After adjustment for baseline and

**Table 1** General demographic characteristics of study participants

| Variable | HIIT + CV ($n = 12$) | HIIT+Placebo ($n = 11$) | CV ($n = 12$) | Placebo ($n = 11$) | *p*-value |
|---|---|---|---|---|---|
| Age (years) | 26.83±5.82 | 29.09±4.7 | 27.08±4.29 | 29.27±5.12 | 0.525* |
| Marital status | | | | | |
| Single1 | 7 (588%) | 5 (45%) | 6 (50%) | 7 (64%) | 0.822** |
| Married | 5 (42%) | 5 (45%) | 5 (42%) | 4 (36%) | |
| Divorced/Widow | 0 | 1 (10%) | 1 (8%) | 0 | |
| Education | | | | | |
| Diploma and lower | 6 (50%) | 2 (18%) | 3 (25%) | 1 (9%) | 0.045** |
| Bachelors and higher | 6 (50%) | 9 (82%) | 9 (75%) | 10 (91%) | |

Age and Physical activity are presented as Mean±SD; other variables are presented as *n* (%)

*HIIT* High intensity interval training, *CV Chlorella vulgaris*

**P* based on ANOVA for continuous variables; ***P* based on chi-square test for categorical variables

**Table 2** Anthropometric characteristics of study participants at baseline and after 8 weeks intervention

| Characteristic | HIIT+CV ($n = 12$) | HIIT+Placebo ($n = 11$) | CV ($n = 12$) | Placebo ($n = 11$) | $P$-value |
|---|---|---|---|---|---|
| Height (cm) | 162.5±8.22 | 159.63±5.4 | 163.54±4.6 | 160±4.75 | 0.332** |
| Weight (kg) | | | | | |
| Before | 82.15±13.53 | 76.3±6.83 | 79.13±9.84 | 73.3±6.95 | 0.177** |
| After | 82.06±14.87 | 75.7±6.76 | 79.15±9.52 | 73.44±10.43 | 0.208** |
| MD (CI95%), $P$* | -0.21 (-1.26, 0.83), 0.889 | -0.54 (-1.61, 0.52), 0.361 | -0.02 (-1.04, 1.0), 0.968 | 0.28 (-0.81, 1.37), 0.742 | 0.734*** |
| BMI (kg/m2) | | | | | |
| Before | 30.97±3.26 | 29.98±2.90 | 29.51±2.68 | 28.66±2.80 | 0.302** |
| After | 30.90±3.58 | 29.76±2.96 | 29.52±2.56 | 28.71±2.85 | 0.389** |
| MD (CI95%), $P$* | -0.08 (-0.49, 0.33), 0.749 | -0.23 (-0.64, 0.19), 0.360 | 0.01 (-0.38, 0.41), 0.943 | 0.06 (-0.38, 0.41), 0.757 | 0.766*** |
| WC (cm) | | | | | |
| Before | 94.91±8.21 | 92.81±5.77 | 93.54±8.04 | 91.72±7.77 | 0.781** |
| After | 91.25±8.83 | 90.63±6.18 | 91.66±8.27 | 91.77±8.38 | 0.987** |
| MD (CI95%), $P$* | -3.67 (-5.23, -2.11), 0.002 | -2.18 (-3.80, -0.56), 0.013 | -1.88 (-3.42, -0.33), 0.055 | 0.05 (-1.57, 1.67), 0.929 | 0.019*** |
| HC (cm) | | | | | |
| Before | 115.75±5.64 | 111.54±6.36 | 113.250±6.01 | 109.45±2.65 | 0.051** |
| After | 113.66±5.74 | 109.90±6.60 | 111.66±6.73 | 109.09±2.42 | 0.236** |
| MD (CI95%), $P$* | -2.09 (-3.16, -1.03), 0.003 | -1.63 (-2.70, -0.56), 0.001 | -1.59 (-2.60, -0.57), 0.027 | -0.35 (-1.46, 0.76), 0.397 | 0.167*** |
| WHR | | | | | |
| Before | 0.82±0.07 | 0.83±0.05 | 0.82±0.07 | 0.83±0.07 | 0.939** |
| After | 0.80±0.07 | 0.82±0.05 | 0.82±0.06 | 0.84±0.07 | 0.617** |
| MD (CI95%), $P$* | -0.02 (-0.03, -0.01), 0.052 | -0.01 (-0.02, 0.01), 0.355 | -0.01 (-0.02, 0.01), 0.37 | 0.004 (-0.01, 0.02), 0.554 | 0.166*** |

Values are Mean (SD)

*BMI* body mass index, *WC* waist circumference, *HC* hip circumference, *WHR* waist to hip ratio

*$P$ based on Paired samples t-test for intragroup comparisons; ** $P$ based on ANOVA test; *** $P$ based on ANCOVA adjusted for baseline values

confounders serum insulin levels (-4.10 (-5.82, -2.39)) as well as HOMA-IR (-0.813 (-1.16, -0.46)) showed significant reductions in CV+HIIT group in comparison with other groups.

## Discussion

The present clinical trial evaluated the impacts of CV and/or HIIT on anthropometric and metabolic parameters in a number of overweight or obese women. The results showed that CV and/or HIIT (without calorie restriction) had no significant effects on the body weight and BMI. Nevertheless, the consumption of CV along with HIIT significantly reduced the WC value when compared with the placebo group, while HIIT+Placebo and CV alone did not affect WC.

The previous studies have assessed the effects of HIIT or CV supplementation on anthropometric parameters; however, to the best of our knowledge, the combined effects of HIIT and CV supplementation in the women with overweight/obesity have not been studied yet. Despite this, Ebrahimi et al. [23] found that using CV (in the form of four 300 mg tablets of C. vulgaris) for 12 weeks in the patients with non-alcoholic fatty liver disease (NAFLD) resulted in a significant reduction of body weight. In another trial, Panahi et al. [25] also found a statistically significant reduction in the body weight of some NAFLD patients after consuming CV (1200 mg/day). However, we failed to find this considerable improvement, which was partially due to the relatively lower dosage or the shorter duration of the study. Besides, since the energy intake remained unchanged by the end of the study, no remarkable effect on body weight was expected. On the other hand, [12] short-term HIIT and moderate-intensity training (MIT) could improve the body composition status in overweight and obese individuals in the absence of BMI changes. Thus, CV and/or HIIT could induce a reduction in the body fat mass without any accompanying body-weight changes. In this regard, Wewege et al [12] suggested that exercise could induce fat loss, mainly in the abdominal fat, even without weight reduction. Another meta-analysis [30] has concluded that, while the caloric restriction diets were more effective than physical activity on the weight loss, exercise was more influential on the abdominal fat reduction. In another meta-analysis carried out in 2018, following protocols using <90% intensities decreased visceral fat mass, and HIIT led to good outcomes in overweight and obese subjects when normal-weight subjects were excluded [31]. It has been demonstrated that lipolytic hormones such as catecholamines and growth hormones could be increased parallel to exercise intensity, especially HIIT, inducing fat burning in the abdominal area [32, 33]

**Table 3** Dietary intake and physical activity of study participants at baseline and after 8 weeks intervention

| Variable | HIIT+CV ($n = 12$) | HIIT+Placebo ($n = 11$) | CV ($n = 12$) | Placebo ($n = 11$) | $P$-value |
|---|---|---|---|---|---|
| Energy (Cal) | | | | | |
| Before | 1876.00±310.2 | 1760.09±337.0 | 1600.75±215.2 | 1679.09±350.7 | 0.169** |
| After | 1825.08±337.4 | 1773.54±185.7 | 1565.75±320.6 | 1654.72±365.9 | 0.188** |
| MD (CI95%), $P$* | 50.92 (-67.90, 169.73), 0.377 | -13.45 (-137.55, 110.65), 0.870 | 35.00 (-83.82, 153.82), 0.537 | 24.36 (-99.73, 148.46), 0.614 | 0.893*** |
| Protein (g) | | | | | |
| Before | 68.83±14.71 | 58.61±19.09 | 55.97±16.55 | 54.40±10.14 | 0.127** |
| After | 63.04±10.97 | 59.23±12.47 | 54.35±12.43 | 53.22±9.25 | 0.151** |
| MD (CI95%), $P$* | -2.41 (-14.11, 9.29), 0.068 | -7.84 (-20.06, 4.37), 0.881 | 3.29 (-8.41, 14.98), 0.546 | 6.63 (-5.58, 18.85), 0.605 | 0.350*** |
| Carbohydrate (g) | 252.77±51.31 | 224.77±60.52 | 224.15±41.36 | 242.17±63.26 | 0.516** |
| Before | 264.10±61.71 | 261.39±40.31 | 247.62±80.88 | 244.69±96.90 | 0.893** |
| After | -11.33 (-62.27, 39.60), | -52.25 (-105.45, 0.946), | -23.47 (-74.41, 27.46), | -2.52 (-55.72, 50.68), | 0.568*** |
| MD (CI95%), $P$* | 0.571 | 0.132 | 0.355 | 0.926 | |
| Fat (g) | | | | | |
| Before | 67.12±15.56 | 70.11±23.01 | 58.35±18.60 | 58.72±18.62 | 0.356** |
| After | 63.01±11.58 | 57.56±10.18 | 47.12±22.16 | 57.76±24.92 | 0.209** |
| MD (CI95%), $P$* | 13.27 (-2.89, 29.43), 0.207 | 8.91 (-7.97, 25.78), 0.067 | 11.23 (-4.93, 27.39), 0.217 | 0.956 (-15.92, 17.83), 0.928 | 0.734*** |
| Cholesterol (mg) | | | | | |
| Before | 164.94±136.2 | 223.45±207.7 | 197.38±160.7 | 209.71±228.9 | 0.851** |
| After | 231.82±225.95 | 260.60±199.9 | 158.17±213.2 | 80.33±88.40 | 0.144** |
| MD (CI95%), $P$* | -66.87 (-199.19, 65.44), 0.304 | -3.17 (-148.11, 141.77), 0.971 | 39.21 (-93.10, 171.52), 0.532 | 125.38 (-12.82, 263.57), 0.080 | 0.246*** |
| Dietary fiber (g) | | | | | |
| Before | 12.63±5.67 | 13.26±6.08 | 11.17±3.68 | 12.56±5.43 | 0.805** |
| After | 11.63±3.88 | 11.25±3.96 | 16.15±12.12 | 15.67±10.82 | 0.384** |
| MD (CI95%), $P$* | 1.00 (-4.89, 6.89), 0.490 | 2.01 (-4.14, 8.17), 0.344 | -4.98 (-10.87, 0.91), 0.239 | -3.12 (-9.27, 3.03), 0.415 | 0.304*** |
| Physical activity (METS) | | | | | |
| Before | 527.92±487.29 | 284.09±245.72 | 354.08±288.64 | 490.80±427.39 | 0.381** |
| After | 3466.50±2154.20 | 1842.72±308.65 | 184.75±227.20 | 484.00±110.94 | <0.001** |
| MD (CI95%), $P$* | -2938.58 (-4321.9, -1555.2), 0.001 | -1558.64 (-1801.1, -1316.1), <0.001 | 169.33 (27.85, 310.8), 0.023 | 6.80 (-213.96, 227.56), 0.946 | <0.001*** |

Values are Mean (SD)

*$P$ based on Paired samples t-test for intragroup comparisons; ** $P$ based on ANOVA test; *** $P$ based on ANCOVA adjusted for baseline values

The second hypothesis was that CV and/or HIIT could improve the metabolic parameters. In this regard, we showed some significant improvement in the lipid profile following interventions. Our results also showed a remarkable decrease of the TG levels in the intervention groups, as compared with the placebo group, whereas TC levels had no significant change. CV and/or HIIT interventions also resulted in a significant decrease of LDL cholesterol levels; more importantly, CV+HIIT was more effective in reducing LDL cholesterol in comparison to supplementation with CV or HIIT+Placebo. Another interesting finding was that while HIIT with or without CV had remarkable effects on HDL, CV intake alone failed to affect HDL cholesterol. Similar to the present study, Ebrahimi et al. [24] showed the significant reduction of the TG level in some NAFLD patients consuming CV (1200 mg/day for 3 months), as compared with controls. A recent meta-analysis [34] also showed that CV had significant effects on the LDL cholesterol level.

However, another meta-analysis [34] found that CV had no significant effect on improving TG . Thus, more specific RCTs in subjects with dissimilar health conditions, particularly those with a high risk of cardiovascular diseases, are warranted to better probe the effect of Chlorella supplementation on cardiovascular risk factors.

The effects of HIIT on the lipid profile were controversial; according to our findings, the 8-week week HIIT improved the lipid profile in overweight and obese women. However, based on a study by Khammassi et al. [35], the HIIT for the same duration did not result in any significant changes in the lipid profile of some overweight and obese young subjects.

**Table 4** Cardiometabolic parameters of study participants at baseline and after 8 weeks intervention

| Variable | HIIT+CV ($n = 12$) | HIIT+Placebo ($n = 11$) | CV ($n = 12$) | Placebo ($n = 11$) | *P*-value |
|---|---|---|---|---|---|
| TG (mg/dL) | | | | | |
| Before | 122.91±41.77 | 132.63±40.84 | 147.91±51.73 | 11.27±32.34 | 0.86 |
| After | 103.58±46.49 | 114±29.50 | 126.50±40.16 | 115.90±25.20 | 0.509 |
| MD (CI95%), *P** | -20.82 (-31.40,-10.23), 0.008 | -17.73 (-28.77,-6.70), 0.018 | -16.77 (-27.61,-5.92), 0.016 | 0.29 (-10.97,11.56), 0.178 | 0.042 |
| TC (mg/dL) | | | | | |
| Before | 179.16±33.51 | 189.09±19.04 | 174.83±23.04 | 162.09±16.86 | 0.086 |
| After | 168.08±35.78 | 186.27±19.01 | 170.16±20.78 | 167.18±18.74 | 0.241 |
| MD (CI95%), *P** | -10.61 (-19.18,-2.03), 0.01 | -0.69 (-9.94,8.56), 0.482 | -4.91 (-13.47,3.64), 0.222 | 2.72 (-6.61,12.05), 0.445 | 0.175 |
| LDL-C (mg/dL) | | | | | |
| Before | 107.08±28.34 | 106.38±17.30 | 99.25±26.72 | 91.10±13.15 | 0.312 |
| After | 88.41±29.17 | 97.74±20.29 | 90.30±24.45 | 96.09±14.16 | 0.726 |
| MD (CI95%), *P** | -17.99 (-24.60,-11.38), 0.001 | -8.04 (-14.92,-1.16), 0.011 | -9.15 (-15.70,-2.60), 0.034 | 3.87 (-3.13,10.87), 0.282 | 0.001 |
| HDL-C (mg/dL) | | | | | |
| Before | 47.50±9.08 | 55.72±10.51 | 46.00±5.78 | 48.72±8.69 | 0.052 |
| After | 60.16±6.86 | 65.27±6.61 | 51.41±11.11 | 50.63±11.56 | 0.001 |
| MD (CI95%), *P** | 12.18 (8.17,16.20), 0.001 | 11.18 (6.72,15.63), 0.016 | 4.55 (0.47,8.63), 0.066 | 1.74 (-2.42,5.91), 0.194 | 0.002 |
| AIP | | | | | |
| Before | 0.39±0.182 | 0.36±0.196 | 0.48±0.17 | 0.34±0.18 | 0.262 |
| After | 0.20±0.183 | 0.23±0.145 | 0.38±0.20 | 0.36±0.17 | 0.047 |
| MD (CI95%), *P** | -0.19 (-0.24,-0.15), <0.001 | -0.14 (-0.19,-0.09), 0.001 | -0.09 (-0.14,-0.05), <0.001 | 0.007 (-0.04,-0.056), 0.423 | <0.001 |
| LAP | | | | | |
| Before | 53.15±27.37 | 52.32±19.31 | 58.76±22.49 | 43.61±18.19 | 0.450 |
| After | 40.96±27.36 | 42.16±15.40 | 48.30±18.78 | 45.04±17.28 | 0.822 |
| MD (CI95%), *P** | -12.02 (-16.97,-7.06), <0.001 | -10.13 (-15.31,-4.95), 0.001 | -9.36 (-14.38,-4.35), 0.022 | -9.36 (-14.38,-4.35), 0.293 | 0.010 |
| VAI | | | | | |
| Before | 5.13±2.27 | 4.67±1.87 | 6.32±2.76 | 4.54±1.78 | 0.215 |
| After | 3.20±1.69 | 3.23±0.91 | 4.95±2.27 | 4.64±1.75 | 0.031 |
| MD (CI95%), *P** | -1.95 (-2.38,-1.52), <0.001 | -1.59 (-2.05,-1.14), 0.002 | -1.04 (-1.49,-0.60), <0.001 | -0.09 (-0.54,0.37), 0.496 | <0.001 |

Values are Mean (SD)

*TC* total cholesterol, *TG* Triglycerides, *AIP* atherogenic index of plasma, *AC* atherogenic coefficient, *LAP* lipid accumulation product, *VAI* visceral adiposity index

**P* based on Paired samples t-test for intragroup comparisons; ***P* based on ANOVA test; ****P* based on ANCOVA adjusted for baseline values

In a meta-analysis, Batacan et al. [36] also concluded that long-term HIIT did not affect lipid profiles in overweight/obese populations.

Several factors might account for these discrepancies; these include age, gender, the obesity degree (moderate, severe or morbid), the diversity of training programs, or the measurement techniques used.

The existing results, thus, highlight CV and/or HIIT could make significant improvement by reducing the cardiometabolic risk factors. Indeed, the comparison of groups showed significant meaningful improvement in the levels of AIP, VAI, and LAP in our intervention groups (as compared with the control one) ($p < 0.05$). These changes can have effective clinical and health-related consequences. Indeed, VAI has a greater power to detect unhealthy metabolic phenotypes from the conventional parameters [37]; LAP can properly discriminate individuals with pre-diabetes or diabetes [38]; also, AIP is positively related to all-cause mortality [39]. This suggests that our interventions might reduce the incidence risk of cardio-metabolic diseases in overweight/obese women.

CV is a great source of such carotenoids as lutein, zeaxanthin, alpha and beta carotene. It seems that an increase in carotenoids following CV supplementation can suppress the LDL cholesterol receptors located on the cell membranes and cholesterol bio-synthase pathway. Instead, carotenoids

**Table 5** Glycemic parameters of study participants at baseline and after 8 weeks intervention

| Variable | HIIT+CV ($n = 12$) | HIIT+Placebo ($n = 11$) | CV ($n = 12$) | Placebo ($n = 11$) | $P$-value |
|---|---|---|---|---|---|
| FBS (mg/dL) | | | | | |
| Before | 81.58±6.63 | 83.18±6.46 | 82.83±9.29 | 80.63±7.81 | 0.853** |
| After | 82.16±7.70 | 81.18±7.33 | 83.33±7.92 | 82.45±7.56 | 0.926** |
| MD (CI95%), $P$* | 0.46 (-2.51,3.44), 0.754 | -1.72 (-4.84,1.39), 0.306 | 0.69 (-2.29,3.67), 0.663 | 0.69 (-2.29,3.67), 0.248 | 0.510*** |
| Insulin (μIU/ml) | | | | | |
| Before | 21.07±7.29 | 16.14±4.37 | 18.22±6.66 | 15.85±5.91 | 0.171** |
| After | 15.54±4.86 | 16.42±3.97 | 16.21±4.47 | 16.73±4.32 | 0.930** |
| MD (CI95%), $P$* | -4.10 (-5.82,-2.39), 0.001 | -0.51 (-2.26,1.24), 0.837 | -1.87 (-3.53,-0.21), 0.049 | -0.04 (-1.79,1.72), 0.429 | 0.011*** |
| HOMA-IR | | | | | |
| Before | 4.22±1.36 | 3.31±0.97 | 3.74±1.44 | 3.14±1.20 | 0.187** |
| After | 3.15±0.99 | 3.27±0.81 | 3.34±1.00 | 3.38±0.88 | 0.938** |
| MD (CI95%), $P$* | -0.813 (-1.16,-0.46), 0.001 | -0.17 (-0.52,0.19), 0.888 | -0.34 (-0.68,-0.01), 0.088 | 0.04 (-0.32,0.4), 0.286 | 0.012*** |

Values are Mean (SD)

*Obtained from ANCOVA adjusted for baseline

*$P$ based on Paired samples t-test for intragroup comparisons; **$P$ based on ANOVA test; ***$P$ based on ANCOVA adjusted for baseline values

increase the LDL cholesterol receptors in the macrophage organelles and develop their capacity for LDL cholesterol scavenging in the plasma, resulting in the decrease of the LDL cholesterol concentration in plasma [17, 40].

In our study, we showed that CV supplementation and/or HIIT had no significant beneficial effects on FBS. CV or HIIT had no significant effect on the serum levels of insulin and consequently, HOMA-IR; co-administration, however, had beneficial effects. It can be, therefore, hypothesized that higher doses (e.g.: 1200 mg/day) of CV are required for significant effects on FBS [23]. There are, however, few clinical trials investigating the effects of CV on the glycemic status. Despite this, some animal studies have reported the hypoglycemic effects of CV [41] by enhancing the cellular glucose uptake and decreasing non-estrificated fatty acid (NEFA) levels [22]. In a similar animal study [16], it was found that CV had no significant effect on the insulin secretion stimulated by blood glucose; however, it was associated with significant insulin sensitivity improvement in type 2 diabetic and normal rats. Despite this, CV in diabetic rats failed to show any hypoglycemic effect, which could be attributed to the shorter duration of the intervention [19]. In another clinical trial, consumption of CV by high-risk subjects led to the enhancement of glucose metabolism and a great inclination toward glucose concentrations [42]. It seems, therefore, that CV could enhance glucose uptake [41] and mitigate NEFA levels [22], consequently ameliorating hyperglycemia in those populations with risk factors or diabetic patients. Due to the insufficient evidence on other glycemic markers (glycosylated hemoglobin, insulin and insulin resistance indicators), no definite conclusion could be drawn regarding the effect of CV on glucose metabolism. Further studies investigating the impacts of CV on glycemic control metrics can address this question.

An animal study [43] also investigated the metabolic effects of swimming exercise after 14 days of CV supplementation. The results indicated the repressed oxidoreductase enzyme activity and the leukotriene synthesis cascade. Another study conducted by Horri et al. [26] also revealed that the combined CV intake with or without aerobic exercise training enhanced glycemic control in T2DM rats; further, a combined intervention had a more beneficial effect. Similar to our results, Lee et al. recently reported no significant impact on glycemic control based on a 12-week HIIT intervention in T1D adults [44]. In contrast, HIIT showed beneficial effects on the glycemic control in prediabetes [45]. Thus, it can be concluded that supplementation or training responses are dependent on the baseline health status, various dosages, and training protocols. Samadi et al. [46] also showed the greater modulating effects of CV and intense acute eccentric exercise on insulin resistance in some overweight men. In addition, Horii et al. [47] reported that compared with HIIT and CV alone, the combination approach exerted a more pronounced effect on muscle glycolytic and oxidative metabolism.

HIIT, therefore, appears to be effective in glycemic control improvement, particularly in high-risk or affected T2DM [48]. Besides this, insulin sensitivity improvement following reduced exertion high intensity interval training (REHIT) is sex-specific, as shown in a study carried out by Richard et al. [49]; there was no improvement in insulin sensitivity in women following the training program performance. In contrast, a prior study [50] did not find gender differences in regard to insulin sensitivity improvements among active volunteers following 2 weeks of the classic HIT. To date, there has been no study evaluating the effects of HIT on insulin sensitivity in women. Despite this, adherence to a traditional aerobic training program in a great cohort [51] showed a greater insulin sensitivity improvement in the men,

as compared with women. It is, therefore, suggested that the baseline level of insulin sensitivity could affect the subsequent training response [49].

HIIT is associated with improved insulin resistance via regulating some metabolic pathways including glucose transporter 4 (GLUT-4) content [52] and muscle glycogen stores depletion-induced insulin sensitivity [49]. In addition, some studies on obese and diabetic animals have shown that CV can restore the damage of muscle protein kinase B (PKB, also recognized as Akt) phosphorylation [53], and GLUT4 protein synthesis [18]. Thus, the molecular mechanism of muscle Akt and GLUT4 signaling activation may be identical to that of exercise and training. There is evidence that CV intake in combination with aerobic exercise can stimulate muscle PI3K, Akt and GLUT4 signaling in T2DM rats more than the time when CV intake or exercise training is done alone. Thus, a combination of CV supplementation and exercise training might have extra or synergistic effects on the stimulation of muscle PI3K, Akt and GLUT4 signaling, leading to the better management of hyperglycemia in the patients with T2DM [26].

## Strength and limitations

A combination of HIIT and CV as an adjunctive therapy in obesity had not been previously investigated, showing the novelty of our study design. Of course, the present study had some limitations, such as the inability to recommend a proper dose for CV supplementation in obesity treatment. Therefore, other studies with different doses of CV are required. Low motivation of obese and inactive women to participate in the exercise program and low space compelled us to include few individuals in the study. On the other hand, the results of this study cannot be generalized to both sexes. Finally, this intervention was short in duration.

## Conclusion

This study indicated that CV and HIIT could independently and synergistically induce clinically significant improvements in the metabolic profile of the women with overweight/obesity along with minimal side-effects. Our results also suggested that the primary degree of obesity might affect the effectiveness of such interventions. So further studies are needed to improve weight loss strategies.1

**Author's contributions** M.S contributed in conception, design, statistical analysis and drafting of the manuscript. A.B contributed in design and drafting of the manuscript and supervised the study. M.K supervised the exercise program. A.I and FHS contributed in statistical analysis and manuscript drafting. R.A helped for the editing and improving the manuscript. All authors approved the final version for submission.

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## Declarations

**Conflicts of interest** None of the authors had any conflict of interests.

## References

1. Kinlen D, Cody D, O'Shea D. Complications of obesity. QJM: An Int J Med. 2018;111(7):437-43.
2. Djalalinia S, Saeedi Moghaddam S, Sheidaei A, Rezaei N, Naghibi Iravani SS, Modirian M, et al. Patterns of Obesity and Overweight in the Iranian Population: Findings of STEPs 2016. Front Endocrinol. 2020;11(42).
3. Afshin A, Forouzanfar M, Reitsma M, Sur P, Estep K, Lee A, et al. Health effects of overweight and obesity in 195 countries over 25 years: The GBD 2015 Obesity Collaborators. N Engl J Med. 2017;377(1):13–27.
4. Jafari-Adli S, Jouyandeh Z, Qorbani M, Soroush A, Larijani B, Hasani-Ranjbar S. Prevalence of obesity and overweight in adults and children in Iran; a systematic review. J Diabetes Metab Disord. 2014;13(1):1–10.
5. Heymsfield SB, Wadden TA. Mechanisms, pathophysiology, and management of obesity. N Engl J Med. 2017;376(3):254–66.
6. Dubbert PM, Carithers T, Hall JE, Barbour KA, Clark BL, Sumner AE, et al. Obesity, physical inactivity, and risk for cardiovascular disease. Am J Med Sci. 2002;324(3):116–26.
7. Hallal PC, Andersen LB, Bull FC, Guthold R, Haskell W, Ekelund U, et al. Global physical activity levels: surveillance progress, pitfalls, and prospects. The Lancet. 2012;380(9838):247–57.
8. Wing RR. Behavioral approaches to the treatment of obesity. Handbook of obesity: Clinical applications. 2004;2:147–67.
9. Petridou A, Siopi A, Mougios V. Exercise in the management of obesity. Metabolism. 2019;92:163–9.
10. Satariano WA, Haight TJ, Tager IB. Reasons given by older people for limitation or avoidance of leisure time physical activity. J Am Geriatr Soc. 2000;48(5):505–12.
11. Kushner RF. Weight loss strategies for treatment of obesity. Prog Cardiovasc Dis. 2014;56(4):465–72.
12. Wewege M, Van Den Berg R, Ward R, Keech A. The effects of high-intensity interval training vs. moderate-intensity continuous training on body composition in overweight and obese adults: a systematic review and meta-analysis. Obes Rev. 2017;18(6):635-46.
13. Obert J, Pearlman M, Obert L, Chapin S. Popular weight loss strategies: a review of four weight loss techniques. Curr Gastroenterol Rep. 2017;19(12):61.
14. Zaer Ghodsi N, Zolfaghari MR, Fattah A. The impact of high intensity interval training on lipid profile, inflammatory markers and anthropometric parameters in inactive women. Med Lab J. 2016;10(1):56–60.
15. Lee SH, Kang HJ, Lee H-J, Kang M-H, Park YK. Six-week supplementation with Chlorella has favorable impact on antioxidant status in Korean male smokers. Nutrition. 2010;26(2):175–83.
16. Jeong H, Kwon HJ, Kim MK. Hypoglycemic effect of *Chlorella vulgaris* intake in type 2 diabetic Goto-Kakizaki and normal Wistar rats. Nutr Res Pract. 2009;3(1):23–30.

17. Shibata S, Hayakawa K, Egashira Y, Sanada H. Hypocholesterolemic mechanism of Chlorella: Chlorella and its indigestible fraction enhance hepatic cholesterol catabolism through up-regulation of cholesterol 7α-hydroxylase in rats. Biosci Biotechnol Biochem. 2007;71(4):916–25.
18. Lee HS, Kim MK. Effect of *Chlorella vulgaris* on glucose metabolism in Wistar rats fed high fat diet. J Med Food. 2009;12(5):1029–37.
19. Aizzat O, Yap S, Sopiah H, Madiha M, Hazreen M, Shailah A, et al. Modulation of oxidative stress by *Chlorella vulgaris* in streptozotocin (STZ) induced diabetic Sprague-Dawley rats. Adv Med Sci. 2010;55(2):281–8.
20. Kwak JH, Baek SH, Woo Y, Han JK, Kim BG, Kim OY, et al. Beneficial immunostimulatory effect of short-term Chlorella supplementation: enhancement of Natural Killercell activity and early inflammatory response (Randomized, double-blinded, placebo-controlled trial). Nutr J. 2012;11(1):53.
21. Cherng J-Y, Shih M-F. Preventing dyslipidemia by Chlorella pyrenoidosa in rats and hamsters after chronic high fat diet treatment. Life Sci. 2005;76(26):3001–13.
22. Cherng J-Y, Shih M-F. Improving glycogenesis in Streptozocin (STZ) diabetic mice after administration of green algae Chlorella. Life Sci. 2006;78(11):1181–6.
23. Ebrahimi-Mameghani M, Sadeghi Z, Farhangi MA, Vaghef-Mehrabany E, Aliashrafi S. Glucose homeostasis, insulin resistance and inflammatory biomarkers in patients with non-alcoholic fatty liver disease: Beneficial effects of supplementation with microalgae *Chlorella vulgaris*: A double-blind placebo-controlled randomized clinical trial. Clin Nutr. 2017;36(4):1001–6.
24. Ebrahimi-Mameghani M, Aliashrafi S, Javadzadeh Y, Asghari-Jafarabadi M. The Effect of *Chlorella vulgaris* Supplementation on Liver Enzymes, Serum Glucose and Lipid Profile in Patients with Non-Alcoholic Fatty Liver Disease. Health Promot Perspect. 2014;4(1):107–15.
25. Panahi Y, Ghamarchehreh ME, Beiraghdar F, Zare R, Jalalian HR, Sahebkar A. Investigation of the effects of *Chlorella vulgaris* supplementation in patients with non-alcoholic fatty liver disease: a randomized clinical trial. Hepato-Gastroenterology. 2012;59(119):2099–103.
26. Horii N, Hasegawa N, Fujie S, Uchida M, Iemitsu K, Inoue K, et al. Effect of combination of chlorella intake and aerobic exercise training on glycemic control in type 2 diabetic rats. Nutrition. 2019;63:45–50.
27. Amato MC, Giordano C, Galia M, Criscimanna A, Vitabile S, Midiri M, et al. Visceral adiposity index (VAI): a reliable indicator of visceral fat function associated with cardiometabolic risk. Diabetes Care. 2010.
28. Kahn HS. The" lipid accumulation product" performs better than the body mass index for recognizing cardiovascular risk: a population-based comparison. BMC Cardiovasc Disord. 2005;5(1):26.
29. Niroumand S, Khajedaluee M, Khadem-Rezaiyan M, Abrishami M, Juya M, Khodaee G, et al. Atherogenic index of plasma (AIP): a marker of cardiovascular disease. Med J Islam Repub Iran. 2015;29:240.
30. Verheggen R, Maessen M, Green DJ, Hermus A, Hopman M, Thijssen D. A systematic review and meta-analysis on the effects of exercise training versus hypocaloric diet: distinct effects on body weight and visceral adipose tissue. Obes Rev. 2016;17(8):664–90.
31. Maillard F, Pereira B, Boisseau N. Effect of high-intensity interval training on total, abdominal and visceral fat mass: a meta-analysis. Sports Med. 2018;48(2):269–88.
32. Pritzlaff CJ, Wideman L, Blumer J, Jensen M, Abbott RD, Gaesser GA, et al. Catecholamine release, growth hormone secretion, and energy expenditure during exercise vs. recovery in men. J Appl Physiol. 2000;89(3):937-46.
33. Zhang H, Tong TK, Qiu W, Zhang X, Zhou S, Liu Y, et al. Comparable effects of high-intensity interval training and prolonged continuous exercise training on abdominal visceral fat reduction in obese young women. J Diabetes Res. 2017;2017.
34. Fallah AA, Sarmast E, Dehkordi SH, Engardeh J, Mahmoodnia L, Khaledifar A, et al. Effect of Chlorella supplementation on cardiovascular risk factors: A meta-analysis of randomized controlled trials. Clin Nutr. 2018;37(6):1892–901.
35. Khammassi M, Ouerghi N, Hadj-Taieb S, Feki M, Thivel D, Bouassida A. Impact of a 12-week high-intensity interval training without caloric restriction on body composition and lipid profile in sedentary healthy overweight/obese youth. J Exerc Rehab. 2018;14(1):118.
36. Batacan RB, Duncan MJ, Dalbo VJ, Tucker PS, Fenning AS. Effects of high-intensity interval training on cardiometabolic health: a systematic review and meta-analysis of intervention studies. Br J Sports Med. 2017;51(6):494–503.
37. Ferreira FG, Juvanhol LL, da Silva DCG, Longo GZ. Visceral adiposity index is a better predictor of unhealthy metabolic phenotype than traditional adiposity measures: results from a population-based study. Public Health Nutr. 2019;22(9):1545–54.
38. Ahn N, Baumeister SE, Amann U, Rathmann W, Peters A, Huth C, et al. Visceral adiposity index (VAI), lipid accumulation product (LAP), and product of triglycerides and glucose (TyG) to discriminate prediabetes and diabetes. Sci Report. 2019;9(1):1–11.
39. Bendzala M, Sabaka P, Caprnda M, Komornikova A, Bisahova M, Baneszova R, et al. Atherogenic index of plasma is positively associated with the risk of all-cause death in elderly women. Wien Klin Wochenschr. 2017;129(21–22):793–8.
40. Ryu NH, Lim Y, Park JE, Kim J, Kim JY, Kwon SW, et al. Impact of daily Chlorella consumption on serum lipid and carotenoid profiles in mildly hypercholesterolemic adults: a double-blinded, randomized, placebo-controlled study. Nutr J. 2014;13(1):57.
41. Jong-Yuh C, Mei-Fen S. Potential hypoglycemic effects of Chlorella in streptozotocin-induced diabetic mice. Life Sci. 2005;77(9):980–90.
42. Mizoguchi T, Takehara I, Masuzawa T, Saito T, Naoki Y. Nutrigenomic studies of effects of Chlorella on subjects with high-risk factors for lifestyle-related disease. J Med Food. 2008;11(3):395–404.
43. Mizoguchi T, Arakawa Y, Kobayashi M, Fujishima M. Influence of Chlorella powder intake during swimming stress in mice. Biochem Biophys Res Commun. 2011;404(1):121–6.
44. Lee AS, Johnson NA, McGill MJ, Overland J, Luo C, Baker CJ, et al. Effect of high-intensity interval training on glycemic control in adults with type 1 diabetes and overweight or obesity: a randomized controlled trial with partial crossover. Diabetes Care. 2020.
45. RezkAllah SS, Takla MK. Effects of Different Dosages of Interval Training on Glycemic Control in People With Prediabetes: A Randomized Controlled Trial. Diabetes Spectr. 2019;32(2):125–31.
46. Samadi M, Shirvani H, Shafeie AA. Effect of Chlorella vulgaris supplementation with eccentric exercise on serum interleukin 6 and insulin resistance in overweight men. Sport Sciences for Health. 2020, 16: 543–549.
47. Horii N, Hasegawa N, Fujie S, Uchida M, Miyamoto-Mikami E, Hashimoto T, et al. High-intensity intermittent exercise training with chlorella intake accelerates exercise performance and muscle glycolytic and oxidative capacity in rats. Am J Physiol Regul Integr Comp Physiol. 2017;312(4):R520–8.
48. Jelleyman C, Yates T, O'Donovan G, Gray LJ, King JA, Khunti K, et al. The effects of high-intensity interval training on glucose regulation and insulin resistance: a meta-analysis. Obes Rev. 2015;16(11):942–61.
49. Metcalfe RS, Babraj JA, Fawkner SG, Vollaard NB. Towards the minimal amount of exercise for improving metabolic health: beneficial effects of reduced-exertion high-intensity interval training. Eur J Appl Physiol. 2012;112(7):2767–75.

50. Richards JC, Johnson TK, Kuzma JN, Lonac MC, Schweder MM, Voyles WF, et al. Short-term sprint interval training increases insulin sensitivity in healthy adults but does not affect the thermogenic response to β-adrenergic stimulation. J Phys. 2010;588(15):2961–72.
51. Boulé NG, Weisnagel SJ, Lakka TA, Tremblay A, Bergman RN, Rankinen T, et al. Effects of exercise training on glucose homeostasis: the HERITAGE Family Study. Diabetes Care. 2005;28(1):108–14.
52. Hood MS, Little JP, Tarnopolsky MA, Myslik F, Gibala MJ. Low-volume interval training improves muscle oxidative capacity in sedentary adults. Medi Sci Sports Exerc. 2011;43(10):1849–56.
53. Vecina JF, Oliveira AG, Araujo TG, Baggio SR, Torello CO, Saad MJA, et al. Chlorella modulates insulin signaling pathway and prevents high-fat diet-induced insulin resistance in mice. Life Sci. 2014;95(1):45–52.