High-intensity Interval Training Improves Lipocalin-2 and Omentin-1 Levels in Men with Obesity

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HIIT, lipid profile, body composition, insulin resistance

ABSTRACT
We investigated the effects of 12 weeks of high-intensity interval training (HIIT) on selected circulating adipokines and other cardiovascular diseases risks factors in men with obesity. Thirty men with obesity (age: 24.96 ± 3.11 year, BMI: 30.92 ± 1.04 kg/m²) were randomly assigned to HIIT and control groups. The HIIT group participated in a 12-week HIIT program (5 × 2 min interval bout at an intensity of 85–95 % HRmax interspersed by 1 min passive recovery, three times per week), while the control group maintained their usual lifestyles. Blood lipids, insulin resistance, and select serum adipokines were assessed before and after 12 weeks of the intervention period. HIIT improved body composition and lipid profiles (p < 0.05) and also decreased fasting insulin levels (p = 0.001) and HOMA-IR (p = 0.002) levels. Furthermore, HIIT increased levels of lipocalin-2 (p = 0.002) while decreasing omentin-1 levels (p = 0.001) in men with obesity. Changes in lcn2 and omentin-1 concentrations correlated with the changes in risk factors in the HIIT group (p < 0.05). The results indicate that 12 weeks of supervised HIIT significantly improves both circulating concentrations of lcn2 and omentin-1, two recently described adipokines, and risk markers of cardiovascular diseases in men with obesity. Further research is necessary to understand the molecular mechanisms involved with these changes.
Introduction

Obesity is a complex and multifactorial disease [1], with an escalating global prevalence over the last three decades [1]. Obesity is also a risk factor for many chronic diseases such as metabolic syndrome, type 2 diabetes, and several cancers [1, 2], as well as many cardiovascular diseases [1]. The metabolic abnormalities associated with obesity are partly linked to an imbalance in the secretion of adipokines from adipose tissue [3].

Lipocalin-2 (lcn2), also known as neutrophil gelatinase-associated lipocerin, is a 25 kDa secretory glycoprotein [4]. Lcn2 is a novel adipokine with pro-inflammatory effects that has been implicated in metabolic and inflammatory disorders [4]. The expression and circulating levels of lcn2 are augmented in individuals with obesity and positively associated with the development of insulin resistance and obesity-related metabolic disorders [4]. To this end, obesity-induced increases of lcn2 levels are suggested to be novel and sensitive predictors of cardiovascular diseases (CVD) [5].

Additionally, omentin-1 (also known as intelectin-1) is another novel adipokine (34 kDa) that is mainly expressed in visceral fat [6]. Omentin-1 has anti-inflammatory effects in obesity-related cardiometabolic disorders [7, 8], and plasma levels of omentin-1 and the adipose tissue gene expression levels are decreased in individuals with obesity [6, 8]. In fact, omentin-1 levels are negatively associated with obesity markers such as body mass index (BMI) and waist circumference (WC) [7, 8]. The decreased omentin-1 expression is implicated in several chronic inflammatory diseases [8] and also in obesity-induced insulin resistance development [9].

High-intensity interval training (HIIT) is an alternative to traditional exercise programs with higher adherence rates in adults with overweight/obesity [10]. A recent meta-analysis concluded that HIIT improves cardio-metabolic risk factors and insulin sensitivity in populations with overweight/obesity [11]. Additionally, HIIT provides superior benefits on glycemic control and cardiorespiratory fitness as well as lower ratings of perceived exertion (RPE) scale of Borg compared to moderate-intensity continuous aerobic training [12, 13]. However, there is a dichotomy regarding the effects of HIIT on some adipokines in individuals with overweight/obesity [14–16]. For instance, a study by Madsen et al. (2015) [17] reported that an eight-week HIIT program improved circulating omentin-1 levels, while a study by Nikseresht and colleagues (2016) failed to show improvements in omentin-1 levels after twelve weeks of moderate interval training in the men with obesity [18]. Likewise, Choi et al. (2009) reported unchanged levels of lcn2 levels in females with obesity after twelve weeks of combined exercise training (aerobic and resistance) [9]. In addition, recently, Nakai et al. (2021) showed that 12 weeks of moderate-intensity exercise (40 min, 65% maximal heart rate) or diet could not alter lcn2 in two different cohorts (endurance athletes and individuals with overweight/obesity). A methodological limitation in Nakai et al. ’s study was that they did not use a robust intervention like HIIT or combined aerobic + resistance exercise training in their study [19]. Since it has been shown that high-intensity exercise is highly likely to improve adipokines in individuals with overweight/obesity and with type 2 diabetes; therefore, it could be recognized that the modifications in lcn2 might be more susceptible to exercise intensity than other exercise components [7].

The benefits of HIIT on some of the recently discovered adipokines (such as lcn2 and omentin-1) are poorly described. Furthermore, there are numerous limitations in methodological issues in previous studies, including low participant numbers, varying physical activity abilities of participants, and a wide range of BMI levels, likely accounting for inconsistent findings on the benefits of exercise training (particularly HIIT) in improving adipokine levels in individuals with obesity. Our study examines the influence of HIIT on selected adipokines and other CVD risk factors in a relatively larger group of individuals with obesity to improve these shortcomings. We investigated the effects of 12-weeks of HIIT on lcn2 and omentin-1 concentrations in inactive men with obesity and examined the hypothesis that HIIT leads to beneficial changes in these adipokines concentrations as well as other related CVD risk factors.

Materials and Methods

Participants

Thirty healthy, inactive men with obesity volunteered to participate in this study. Individuals with histories of acute/chronic health conditions such as cardiovascular or metabolic disease and those who smoked tobacco products were excluded from the study. The inclusion criteria were as follows: to be healthy, sedentary (performing < 2 hours of physical activity per week), and BMI = 30–35 kg/m². Participants were informed about the experimental procedures, possible risks, and benefits, and informed consent was obtained before starting the study. The participants were then randomly allocated to either HIIT (n = 15) or control (sedentary; n = 15) groups. All procedures were performed ethically according to international standards as described for the International Journal of Sports Medicine in Harriss et al. (2020) and the latest revision of the Declaration of Helsinki. The Committee on the Use of Human Research Subjects at the Regional Research Ethics Committee of the Islamic Azad University, Mahabad, Iran approved all procedures and the experimental protocols. The participants were asked to maintain their usual eating habits during the training program.

Nutrient intake and dietary analysis

Two-day food records (one weekday and one weekend day) were obtained before and after the study to assess changes in habitual dietary intake over time [21]. Each food item was individually entered into Diet Analysis Plus version 10 (Cengage, Boston, MA), and total energy consumption and the amount of energy derived from proteins, fats, and carbohydrates were determined.

Anthropometry and body composition assessments

Anthropometric and body composition variables (body mass, height, BMI, WC, hip circumference (HC), and waist to hip ratio (WHR)) were evaluated using standard techniques before and at the end of the training protocol. Body mass and heights were measured with light clothing and no footwear after an overnight fast using a digital scale, and the height of the subjects was recorded to the nearest 0.1 cm and weight (nearest 0.1 kg) using a stadiometer. The BMI of each participant was calculated by dividing body mass (kg) by the square of their height (m²). Waist circumference
was measured at the narrowest part of the trunk between the bottom of the rib cage and top of the pelvis, and HC was measured at the largest laterally projecting prominence of the pelvis or pelvic region from the waist to the thigh using a flexible tape measure at the end of a normal expiration. The WHR was calculated as the waist circumference divided by the hip measurement. Fat density (fat mass) was predicted from skin-fold measurements taken on the right side of the body using a specialized skinfold caliper (Baseline Economy ‘Slim-Guide’, USA) at the triceps, abdominal, and suprailliac sites. The percentage of body fat was then estimated using the regression equations described by Brozek et al. [22]. All of the noted measurements were taken by the same trained technician to minimize methodological variations.

**Determination of maximal heart rate (HRmax)**

A computer-based metabolic cart system (Metalyzer 3B, Germany) was used to collect ventilatory expired gases. The equipment was calibrated according to the manufacturer’s recommendations before the start of the measurements. The ergometer was calibrated prior to the start of the test and was accurate to within 1% between 50 and 500 Watts (W). After adjusting the saddle, a 3 min warm-up session was performed on a cycle ergometer (Monark Ergomedic 839E electronic test cycle, Sweden) at 50 W. The work rate was then continuously elevated by 20 W every two minutes until volitional exhaustion. Participants reported their rating of perceived exertion (RPE) using the Borg scale (6–20) during the last volitional exhaustion. Each participant was continuously recorded throughout the test using an HR monitor (Polar, Kempele, Finland). The criteria used for gauging the achievement of a maximal effort and maximal heart rate (HRmax) were: 1) a plateau in VO2 (or failure to increase VO2 by 150 mL·min⁻¹), 2) RER ≥ 1.10, 3) an RPE of ≥ 17 on a 6–20 RPE scale, 4) individuals were no longer able to maintain a pedaling rate of 60 rpm, and 5) reaching a HR ≥ 95% of age-predicted maximal heart rate (HRmax) were: 1) a plateau in VO2 (or failure to increase VO2 by 150 mL·min⁻¹), 2) RER ≥ 1.10, 3) an RPE of ≥ 17 on a 6–20 RPE scale, 4) individuals were no longer able to maintain a pedaling rate of 60 rpm, and 5) reaching a HR ≥ 95% of age-predicted maximal heart rate (208–0.7 × age) [24]. Maximal effort was considered to have been attained if at least three of these five criteria were met or when participants reached the stage of volitional exhaustion. Each participant was asked to maintain a cycling speed of 60 ± 5 (rpm) and was given visual feedback from the Lode control box to continue with the test. The participants were verbally encouraged to exert their maximal efforts throughout the test. After exhaustion, the test continued for more three minutes at a low work rate (30 W) as a cool down period.

**High-intensity interval training protocol**

All participants in the training group underwent a 12-week, supervised HIIT program on three non-consecutive days of the week, while the control group maintained their usual lifestyles and did not perform any unusual strenuous activity. All training sessions were performed on an electronic cycle ergometer (Monark Ergomedic 839E electronic test cycle, Sweden) under the supervision of an experienced physical trainer at the University Athletic and Fitness Center. Each of the prescribed sessions began with a 5 min warm-up period consisting of stretching exercises and continuous cycling at a moderate intensity corresponding to 40–50% of each participant’s HRmax. This was followed by five intervals bouts of cycling exercise (each lasting 2 min) at an intensity of 85–95% HRmax [15], followed by 1 minute of passive recovery between each bout. The HIIT started with 85% of HRmax during the first four weeks with 1 min passive recovery periods between each exercise bout and increased by 5% in each subsequent 4-week period so that the intensity of training reached 95% HRmax with 1 min passive recovery between each exercise bout at the end of the 12th week. At the end of each training session, there was a 5-minute cool-down period involving slow cycling and gentle stretching. Heart rates were monitored during the training sessions with a heart rate monitor (Polar, Kempele, Finland) to maintain the correct training intensity. Individuals were instructed to maintain their exercise intensities at a level necessary to produce a HR between 85–95% of HRmax at a cadence between 120 and 135 RPM during active intervals and 40–50% of HRmax at a cadence of 40–55 RPM during a recovery interval. The adherence rate to the exercise training program was 100%, with all participants completing each of the three training days every week. The participants were advised to consume the same foods two days before the pretest and post-test blood samplings. The first blood sampling (pretest) was obtained 48 hours before the start of training, and the second blood sample was taken at the end of the program (post-test).

**Blood sampling and laboratory measurements**

Blood samples were obtained from the participants’ antecubital vein at baseline and 48 hours after the last training session at the same time (between 7:00 and 9:00 a.m.) after an overnight fast of ten hours. Samples were allowed to clot at room temperature for 10 min and then centrifuged at 3000 g for 15 min at 4°C. Fasting levels of blood glucose, insulin, and lipids were measured immediately. In contrast, serum specimens to measure lcn2 and omentin-1 concentrations were aliquoted into sterile microtubes and frozen at −80°C. Serum concentrations of triglycerides (TG), total cholesterol (TC), and high-density lipoprotein cholesterol (HDL-C) were measured at baseline and end of 12 weeks using an automated clinical chemistry analyzer (Dimension Rxl Max, Siemens Healthcare Diagnostics, Germany). Low-density lipoprotein cholesterol (LDL-C) levels were calculated according to Friedewald et al. [25], where LDL-C = TC - [HDL-C + (TG/5)]. Fasting blood glucose (Glu) concentrations were measured with a modified hexokinase enzymatic method (7020 Clinical Analyzer, Hitachi, Tokyo, Japan), and serum insulin levels were measured using an enzyme-linked immunosorbent assay (ELISA) method (Monobid, California, USA) (intra-Assay CV: 2.1%, inter-Assay CV: 2.4%). Insulin resistance was calculated via the homeostasis model assessment index (HOMA-IR) method: Glu (mmol/L) × fasting insulin (mU/L)/22.5.

Concentrations of lcn2 were measured with an ELISA in duplicate using commercially available kits (Boster Biological Technology Ltd., China). The intra and inter-assay coefficients of variation for lcn2 were < 5.3%, and the sensitivity of the measurements was 0.02 ng/ml. Levels of omentin-1 were determined in duplicate via ELISA kits (Biovendor, Germany). The intra-assay coefficient of variation was 2.8%, and the inter-assay CV was 6.1%, with a sensitivity of 0.12 ng/ml.
Statistical analysis

Data are presented as mean ± standard deviation (SD). A normal distribution of the data was confirmed using the Shapiro–Wilk test, and homogeneity of variance was verified using Levene’s test before statistical analyses were applied. One-way analysis of variance ANOVA was used to evaluate homogeneous groups for anthropometric or physiological parameters at baseline. Paired t-tests were used to compare pre-training and post-training variables in each group (control or training). Two-way (group × time) repeated-measures ANOVA was used to evaluate the effects of exercise training on the dependent variables. Effects sizes (ES) were calculated from ANOVA output by converting partial eta-squared to Cohen’s d [26]. Moreover, within-group ES were computed using the equation ES = (mean post – mean pre)/SD. ES of 0.20–0.60, 0.61–1.19, and ≥ 1.20 were considered as small, moderate, and large, respectively [27]. Pearson’s correlation method was used to calculate correlations between changes in the variables in response to training. All statistical analyses were performed using SPSS statistical software (SPSS version 20.0 for Windows, SPSS Inc., Chicago, IL, USA). The significance level was set at P ≤ 0.05.

Results

Total energy consumption and energy from carbohydrate, fat, and protein were similar in the four groups during the study (p > 0.05) (▶ Table 1). The physiological, body composition and anthropometrical characteristics of the participants before and after the study period are presented in ▶ Table 2. There were no differences in the age, body mass, BMI, and body fat percentage between the training and control groups at the beginning of the study (p > 0.05). Twelve weeks of HIIT decreased body morphology and body composition indices such as weight (p = 0.001; ES: 0.431), BMI (p = 0.001; ES: 0.428), waist circumference (p = 0.001; ES: 0.293), WHR (p = 0.007; ES: 0.302), and body fat percent (p = 0.001; ES: 0.458), while these parameters remained unchanged in the control group (p > 0.05).

Blood chemistry data pre-and post-intervention are presented in ▶ Table 3. Plasma levels of TC (p = 0.007; ES: 0.321) and LDL-C (p = 0.007; ES: 0.288) were reduced, and HDL-C (p = 0.008; ES: 0.302) increased. Likewise, fasting insulin levels (p = 0.001; ES: 0.377) and the insulin resistance index (assessed by HOMA-IR) were decreased (p = 0.002; ES: 0.334) in men with obesity after 12-week of the HIIT program. There were no modifications in TG (p = 0.074) and Glu (p = 0.117) concentration after the training program. Notably, serum lcn2 concentration significantly decreased (p = 0.002; ES: 0.382) in the 12-week HIIT group, while there were no alterations in the control group (p = 0.095). Plasma levels of serum omentin-1 increased after the 12-week of HIIT (p = 0.001; ES: 0.558), while there were no changes in the control group (p = 0.416).

We examined the association between changes in adipokine levels (lcn2 and omentin-1) and changes in cardiovascular risk factors following HIIT. As shown in ▶ Table 4, changes in omentin-1 correlated negatively with CVD risk factors, while changes in lcn2 levels were positively associated with changes in other CVD risk factors (p < 0.05).

Discussion

Lifestyle interventions such as exercise training can help to control weight and attenuate many cardiometabolic risk factors in individuals with obesity. To that end, we examined the effects of HIIT on serum levels of two novel CVD biomarkers, lcn2 and omentin-1, and other cardiovascular risk factors in inactive men with obesity, and we found that 12 weeks of HIIT significantly improves the concentrations of both these adipokines.

Our findings showed that improvements in body composition parameters following a 12-week of HIIT in men with obesity. These findings align with the previous studies showing the beneficial effects of HIIT on body composition in individuals with overweight/obesity [28, 29]. Moreover, a recent meta-analysis concluded that HIIT is a time-efficient alternative that induces greater reductions in body fat percentage compared to traditional exercise programs in adults with [29]. This could partly be attributed to the higher concentration of the catecholamines (which increase lipolysis in adipose tissues through β-adrenoceptor stimulation) and greater metabolic rate and fat expenditure resulting from HIIT compared to moderate-intensity exercise training [30]. Nevertheless, it should also be noted that some studies reported no changes in body composition after the HIIT program in sedentary people [16]. Differences in the participants’ age, health/physical activity status, exercise intensity (i.e., parameters of the HIIT program), and particularly the duration of intervention may underlie the discrepancy between our results and findings of other studies. For example, a 4-week HIIT program may not be sufficient to cause significant changes in body composition in men with obesity in the studies by Alkahtani et al. (2013) [31] and Sasaki et al. (2014) [16]. However, 12-week of HIIT significantly lowered body mass, BMI, and body fat percentage that all are correlated with improvement in lcn2 and omentin-1 in individuals with obesity.

As noted, we found increased circulating omentin-1 levels in men with obesity after a 12-week HIIT program. Insulin resistance (measured by HOMA-IR), fasting insulin levels, and body markers of obesity were inversely related to the plasma levels of omentin-1 [14]. Consistent with our results is a recent study on men with overweight/obesity showing that an 8-week of HIIT increased plasma omentin-1 levels and that the cardiometabolic profile improved (i.e., decreases of HOMA-IR). Similarly, studies by Madsen and colleagues (2015) reported that eight weeks of a HIIT program increased circulating omentin-1 concentrations and caused a reduction in abdominal fat mass as well as improving glycemic control in patients with type 2 diabetes [17]. Furthermore, it has also been reported that 16-weeks of concurrent exercise training (resistance + aerobic) increased serum omentin-1 concentrations in children with obesity, associated with improved insulin sensitivity and weight loss [32]. In addition, we found a negative correlation between omentin-1 and insulin, glucose and HOMA-IR, as well as body fat percentage. It is suggested that serum omentin-1 level decreases with obesity and insulin resistance, and insulin resistance significantly decreased omentin-1 levels [3, 8]. Increased omentin-1 levels in these individuals can increases glucose transfer in the adipose tissue carried out by insulin [33]. Furthermore, omentin-1 is engaged in regulating energy metabolism and the distribution of body fat [33].
Our study indicates that changes in serum omentin-1 are accompanied by changes in body composition and insulin resistance profiles, but we cannot determine if this represents a causal relationship. A potential mechanism for exercise training-induced increases in omentin-1 is likely related to decreases in adipose tissue and weight loss-induced improvements in insulin sensitivity.
[34], which could, in turn, lead to increased omentin-1 gene expression [34]. In addition, omentin-1 levels may increase in response to the physiological adaptation of skeletal muscle due to the release of myokines in response to exercise [35]. In contrast to our observations and those described above, a study by Nikseresht et al. (2016) observed no changes (nonsignificant increase) in serum omentin-1 concentrations in middle-aged men with obesity after 12 weeks of moderate interval training [18]. Although they used vigorous aerobic exercise training (4 × 4-min intervals at 80–90% of maximal heart rate, with each interval separated by 3 min at 65%), it might not be an appropriate exercise program for improving IL-18, RBP-4, and omentin-1 in sedentary individuals with obesity. Likewise, omentin-1 concentrations were unaltered (nonsignificant increase) after three months of aerobic exercise in individuals with obesity [36]. Changes in body composition (i.e., abdominal fat mass and body fat percentage) are essential for improving metabolic abnormalities like insulin resistance or changing adipokines like omentin-1 [3]. However, in the study conducted by AminiLari et al. (2017), insulin did not change in response to 12-week aerobic exercise training. In addition, although body mass and body fat percentage significantly decreased after aerobic exercise training, their reduction was not enough to stimulate an elevation in omentin-1 [36]. In our study we found a greater weight reduction (−3.4% vs. −1%) and fat mass reduction (−8.6% vs. −4.35%) compared to AminiLari et al.’s study. In addition, AminiLari et al. (2017) did not measure WHR in their study; we found a significant decrease in WHR, insulin, and HOMA-IR, which all are involved in improving adipokines levels [8]. The discrepancies between our findings and those reported by others could be explained, in part, by important differences in the intensity of the training program (moderate vs. high intensity), protocol implementation difference (duration and type of training methods), gender, and in the extent of overall body composition changes.

Our findings also show that the serum lnC2 concentrations are reduced after 12 weeks of HIIT in inactive men with obesity. Recent investigations have demonstrated that serum lnC2 levels are higher in subjects with obesity [4,37]. The beneficial influences of exercise training on lnC2 levels could mediate obesity-related metabolic disorders and CVD risks by improving the profile of adipokines secretion [38]. A study conducted by Moghadasi and Mohammadi (2014) also reported that lnC2 levels decreased after eight weeks of resistance or endurance training in sedentary young men, likely due to the anti-inflammatory effects of exercise-related adaptation [39]. In addition, plasma levels of lnC2 decreased after eight weeks of endurance training in men with overweight/obesity [39]. Our findings also support those, demonstrating a direct association between lnC2 levels and body composition change since we found a positive correlation between lnC2 and body mass, BMI as well as body fat percentage [40]. This suggests that exercise-induced decreases in lnC2 levels could be attributed to body fat percentage changes and other body composition parameters. In addition, exercise training on its own has been proposed to reduce levels of nuclear factor-κappa B (NF-κB) that activates adipokines and chemokines [41]. Nonetheless, our results are in contrast with those of Choi et al. (2009), who indicated no changes in serum lnC2 concentrations in females with obesity after 12 weeks of aerobic exercise (45 min/session, 300 kcal/day) and muscle strength training (20 min/session, 100 kcal/day) five times a week [9]. In this study, the aerobic exercise program failed to improve insulin, HOMA-IR, and hsCRP that both are important to improve adipokines like lnC2 and RBP-4 (another member of the lipocalin family), while they reported a significant decrease in body composition variables. Besides, the differences in sex (lnC2 expression is sex-specific in mice), different genetic background (lnC2 levels are principally under genetic control), and, in particular, the intensity of exercise training (moderate vs. high intensity) may explain the discrepancy in exercise-induced changes in plasma adipokines levels [12,29]. Additionally, recent study by Nakai et al. (2021) reported that circulating lnC2 expression remained stable after 12 weeks of moderate-intensity exercise training (65% maximal heart rate for 40 min) in adults with overweight/obesity [19]. However, it should be noted that adipokine levels are more likely to be improved by high-intensity exercise training rather than moderate-intensity exercise training and that modifications in lnC2 might be more susceptible to exercise intensity than other exercise components such as the type and time of exercise training [8]. Therefore,
we speculate that the higher intensity of our exercise training program was an important factor increasing Lcn2 levels. However, more detailed studies are required to understand the exact relationship between fitness, body composition, and Lcn2 levels.

There are several limitations to our study to consider. The first is the lack of stringent dietary and energy expenditure controls, which could affect many of the physiologic variables that can modulate adipokines release. Although we have used a relatively larger number of participants, we presume that we would find more robust effect sizes and statistical power if we recruited more participants. Furthermore, we estimated body fat percentage by using the skinfold thickness method, which is certainly less accurate than a more direct assessment utilizing a dual-energy X-ray absorptiometry (DEXA) or magnetic resonance imaging (MRI) scan [42]. Finally, the current study involved only men and not women.

Conclusions

We report that 12-weeks of HIIT induced improvements in body composition, insulin resistance, lipid profiles, and the serum levels of two critical adipokines (Lcn2 and omentin-1) associated with CVD and inflammation indicators in inactive men with obesity. Our results support the view that HIIT may be an effective non-medical therapeutic strategy to reduce CVD risk factors and obesity-induced disorders. Further studies are needed to understand the exact mechanisms of adipokine changes in response to exercise training in different populations and determine whether serum Lcn2 and omentin-1 levels can serve as predictive biomarkers of CVD risk status.

Contribution Statement

Sirvan Atashak: conceptualization, data collection, formal analysis. Stephen R. Stannard: statistical analysis and conceptualization. Ali Daraei: data interpretation, manuscript preparation and literature search. Mohammad Soltani: data interpretation, manuscript preparation and literature search. Ayoub Saeid: investigation, data collection and conceptualization. Fatah Moradi: investigation and conceptualization. Ismail Laher: resources and data interpretation. Anthony C. Hackney: resources and data interpretation, supervision. Hassane Zouhal: conceptualization, supervision, writing - original draft.

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Conflict of Interest

The authors declare that they have no conflict of interest.
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