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Original research

Effect of swimming training on levels of asprosin, lipid profile, glucose and insulin resistance in rats with metabolic syndrome

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ABSTRACT

Background: Asprosin is a novel biomarker that associated with type 2 diabetes mellitus. The aim of this study was to investigate the effects of continuous and interval swimming training on the asprosin, lipid profile, glucose concentration and insulin resistance serum levels of rats with metabolic syndrome.

Methods: Forty-eight male Wistar rats were randomly divided into two groups, standard diet (SD) and high-fat diet (HD), and received their respective diets for a period of 12 weeks without exercise stimuli. After this period, the animals were randomly divided into four groups (n = 8); normal control standard diet (NC), control (Ctr), continuous training (load 0–3% body mass, 5 d/wk, for 8 weeks, CT) and interval training (load 5–16% body mass, 5 d/wk, for 8 weeks, IT). The continuous and interval training consisted of a swimming exercise performed over eight weeks.

Result: The NC and trained groups showed lower values of total cholesterol (TC), triglyceride (TG), low-density lipoprotein (LDL-C) and glucose concentration compared to Ctr group. Serum level of asprosin significantly decreased underlying CT and IT compared to NC and Ctr groups. No significant difference were observed between trained groups.

Conclusion: It seems that both swimming training methodologies are shown to be effective in the serum levels of asprosin, lipid profile and glucose concentration in metabolic syndrome rats.

1. Introduction

The metabolic syndrome (Mets) is associated to abdominal obesity, blood lipid disorders, diabetes, insulin resistance, dyslipidemia, fatty liver (Després and Lemieux, 2006; Rohman et al., 2017), which have also been associated with several chronic diseases such as cancer, cardiovascular diseases (CVDs), chronic kidney diseases (CKDs) (Galassi et al., 2006; Rayyan Assi, Ziv and Dankner, 2019). Several factors are related to the components of Mets, including central obesity, hypertriglyceridemia (TG), low high-density lipoprotein cholesterol (HDL-C), high total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and raised fasting plasma glucose (Tjønna et al., 2018). Previously evidence suggested that obesity and obesity-related metabolic syndrome are primarily responsible for the epidemic of kidney diseases (Nehus and Mitsnefes, 2019). Obesity links to development of Mets, CVD, hypertension, insulin resistance and diabetes (Elnagar et al., 2018; Kurella et al., 2005; Nehus and Mitsnefes, 2019).

It has been well known that adipose tissue can store energy and secrete bioactive adipokines (Booth et al., 2016). Recently, asprosin as new peptide hormone that involved in regulating glucose level has been discovered by Romere et al. (2016). Asprosin is secreted into the bloodstream mainly by the cells of the white adipose tissue (WAT) and targets the liver to fasting-responsive increase plasma glucose and insulin concentration (Wang et al., 2018; Wiecek et al., 2018). Moreover, asprosin has a genetic background of the C-terminal cleavage product as encoded by Fibrillin1 gen (FBN1) (Wang et al., 2018). It has been observed a pathological increasing of asprosin in human and mice with insulin resistance and its loss of functions via immunologic or genetic methods has profound glucose- and insulin-lowering effect secondary to reduce hepatic glucose release (Romere et al., 2016). A limited number of studies have assessed the role of asprosin in diseases related with obesity (Elnagar et al., 2018; Romere et al., 2016; Wang et al., 2018). It has been suggested that therapeutically targeting asprosin may be useful in type 2 diabetes (T2DM) and Mets (Romere et al., 2016).

Reduction of food intake and exercise training are known as non-drug treatment strategies for the control of energy balance and obesity

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Abbreviations

CVDs	cardiovascular diseases
CT	Continuous training
FBN1	Fibrillin1
HDL-C	High density lipoprotein cholesterol
IT	Interval training
LDL-C	Low density lipoprotein cholesterol
Mets	Metabolic syndrome
QUICKI	Quantitative insulin sensitivity check index
TC	Total cholesterol
TG	Triglyceride
T2DM	Type 2 diabetes mellitus
WAT	White adipose tissue

(Rocha et al., 2016). Various methodology of exercise training such as continuous or interval exercise training with low or moderate intensity is well established that result to adaptions on cardiorespiratory and muscular system, fat oxidation and weight loss (Beavers et al., 2018; Rocha et al., 2016). A randomized multicentre trial study demonstrated that exercise training may prevention of the risk factors of the syndrome in men and women diagnosed with the Mets (Tjønna et al., 2018). A previous study showed that the single anaerobic effort increased the level of asprosin and irisin secretion in health subjects (Wiecek et al., 2018). However, the changes of asprosin concentrations in obesity-related Mets and the role of exercise (continuous or interval training) on the outcomes after performed training methods are still unknown. This study aimed to investigate the effects of continuous and interval swimming training on the asprosin, lipid profile, glucose concentration and insulin resistance serum levels of rats with metabolic syndrome.

2. Materials and methods

2.1. Animals and diet

Six-week old male Wistar rat (n = 48, weighed 150–180 g), used in the study. The rats were housed in the Central Animal Facility of Zahedan University of Medical Sciences. They were maintained under standard laboratory conditions in the animal house (light cycle between 6:00 and 18:00 h and at 21 ± 2 °C). The study protocol was approved by Faculty of Medicine Ethics Committee for animal Research (IR.ZAUMS.REC.2018.220).

The various studies have shown similar symptoms to the metabolic syndrome in humans such as hypertension, diabetes, high glucose, obesity and insulin resistance; hence, the experimental design of the current study is commonly used to induce dietetic in rats (Panchal and Brown, 2010; Senaphan et al., 2015).

At first, animals randomly divided in two groups: standard diet group (SD, n = 16) and high-fat diet group (HD, n = 32) for a 12-week period. Rats allowed free access to water and respective diet. This 12-week period was used to induce changes in body mass and metabolic syndrome by high-fat diet. After the end of this period, animals were randomly divided into four intervention groups: normal control (NC, n = 8), control with metabolic syndrome (Ctr-Mets, n = 8), continuous swimming training with metabolic syndrome (CT-Mets, n = 8) and interval swimming training with metabolic syndrome (IT-Mets, n = 8).

2.2. Diet composition

The standard diet (3.05 kcal/g digestible energy) contained 64.4% carbohydrate (starch 54.4% and sucrose 10%), 23.1% protein (casein), 4.8% fat (soy oil), 0.3% vitamins and 7.7% mineral (Behparvar Company-Tehran, Iran). To make high-fat and high-caloric diet based on available resources, for every of 2400 g contained 1518 g the standard dietary powder, 480 g of fat (lard), 360 g of starch, 360 g of sucrose, 24 g cholesterol and 18 g of cholic acid (Rocha et al., 2016; Rostami et al., 2016).

2.3. Physiological and metabolic variables

For indirect measurement computation of body composition via the Lee obesity index (> 310), rats were weighed, and body lengths (anal-to-nasal distance) were measured daily. ([3 square root body weight (g)/nasoanal length (cm)] × 1000) (Hioki et al., 2010; Lee, 1929). Food consumption was measured daily by weighing the amount of chow consumed over a 24 h period. Also, the rats with blood glucose (> 126 mg/dL), lipid profile (HDL lower than 40 mg/dL and triglyceride > 150 mg/dL), confirmed presence as criteria of metabolic syndrome (Rohman et al., 2017). As described by Sena et al., to assess insulin resistance in the fasted state, quantitative insulin-sensitivity check index (QUICKI) were calculated (C. Sena, Barosa, Nunes, Seica and Jones, 2007). QUIKI was measured as $1/[\log (G_0) + \log (I_0)]$, where G_0 is fasting glycaemia ($mg.dl^{-1}$), and I_0 is fasting insulin level ($\mu U.ml^{-1}$) (C. M. Sena et al., 2011). To assess metabolic syndrome indices, eight-rats were sacrificed from SD and HD groups.

2.4. Swimming protocols

Rats were acclimatized to liquid medium for a week, prior to the start of the physical training protocols, gradually increasing intensity and training volume.

The swimming training protocols was conducted during eight weeks, with a weekly frequency of five days. The load intensity was attached to the animal's tail and was individually adjusted in each exercise session according to animal body mass. The progression of load intensity, volume of interval and continuous training were performed as described by Rocha et al. (2016) (Rocha et al., 2016). To test the applicability and necessary adjustments to the training protocols proposed in this study, we did a pilot study on eight rats before. As a previous

Table 1
Schematic representation of continuous and interval training protocols.

Types of swimming protocols			Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8
	a_{CT}	Set	1	1	1	1	1	1	1	1
		Time	30 min	40 min	30 min	40 min	40 min	50 min	50 min	50 min
		Load	0%	0%	1%	1%	2%	2%	3%	3%
	b_{IT}	Set	5	5	5	5	14	14	14	14
		Time	1 min	1 min	1 min	1 min	20 s	20 s	20 s	20 s
		Rest	1 min	1 min	1 min	1 min	10 s	10 s	10 s	10 s
		Load	0–5%	7%	8%	10%	13%	14%	15%	16%

CT: continuous training (a) IT: interval training (b);

At the end of interventions period, animals were euthanized 48 h after the last training session and 8 h fasting. Blood samples were collected and serum was obtained for biochemical analysis.

study indicated that lactate threshold was achieved with loads between 5 and 6% of rat's body mass. Therefore, the continuous protocol used in this study was considered of low/moderate intensity (load between 0 and 3% of body mass) and interval protocol was considered as high intensity (load between 5 and 16% of body mass) (Table 1). After the exercise sessions, rats were dried and returned to the standard conditions. It should be noted that control groups rat (NC and Ctr) were placed in shallow water (without exercise stimulus) for the same duration.

2.5. Serum biochemical analysis

Serum concentrations of asprosin (intra assay: 0.75 ng/mL; sensitive: 0.02 ng/mL, Zell Bio-Germany), insulin (intra assay: 3.3%; sensitive: 0.07 $\mu g\,l^{-1}$, Mercodia-Sweden) and lipid profiles (Pars Azmon-Iran) were analyzed using rat ELISA based on the kit instructions.

2.6. Statistical analysis

After data normality was assessed by the Shapiro-Wilk test, data was be analyzed by One-way ANOVA and Tukey's post hoc test. Given normal distributions, comparisons of body weight and weight test were performed using ANOVA with repeated measures 8×4 (mixed factorial design). The Pearson coefficient of correlation was used to analyze the correlation between all variables. Statistical tests were conducted by SPSS software version 20 and at the significance level of $P < 0.05$.

3. Result

3.1. Metabolic syndrome indices

Rats showed criteria of metabolic syndrome in high-fat diet groups after 12-weeks (Table 2). The results demonstrate an increase in blood sugar (BS) and TG in HD group compared to SD group ($P = < 0.01$) and the level of HDL-C reduced in HD group versus SD group ($P < 0.01$) (see Tables 2 and 3).

3.2. Lee obesity index and QUICKI sensitivity index

The mean and SD of subject's characteristics (age, weight, index of Lee and QUIKLI) are presenteile no difference in QUICKI was seen between groups (Fig. 1, B).

3.3. 3.3. rats weight

As seen in Fig. 2, body weight rose steadily and plateaued after about 2 weeks in all animal groups (they reached ~350 g). In contrast to the NC and Ctr groups, the IT group showed slightly less weight in last week ($P < 0.01$ and $P < 0.01$; respectively). As ANOVA mixed in time factor showed, body weight significant reduce in IT group in 8th week compared to 1st week ($P = 0.01$). While in the CT and NC groups, there was no different in weight during the intervention period. In addition, the body weight of Ctr group showed an increase compared to the beginning of the experiment ($P = 0.02$) (Fig. 2). There was no significant different between other groups ($P > 0.05$).

3.4. Correlation analysis

The correlations between variables are reported in Table 4. The positive associations between Levels asprosin with glucose concentration are shown in Fig. 3 and no associated with other metabolic parameters. Also, no association has been found between asprosin with insulin concentration.

3.5. 3.5. blood biochemistry analyses

As shown in Fig. 4(A–D), compared to the Ctr-Mets, continuous and interval training groups showed lower concentrations of TC, TG and LDL-C ($P = 02$, $P < 0.01$, $P < 0.01$, $P = 0.1$ and $P < 0.01$, $P < 0.01$ respectively) (Fig. 4 A, B and C respectively), while HDL-C concentration was not significantly affected by interventions groups ($P > 0.05$). TG concentration in NC group was less than Ctr-Mets group ($P < 0.01$) (Fig. 4 D). In addition, serum concentration of TC in Ctr group showed 19.69% increase compared to NC group, however this funding was no statistically significant ($P = 0.09$). NO significant changes were observed between trained groups ($P > 0.05$).

Analyze of data showed non-significant different in insulin concentration after 8-weeks of CT and IT groups ($P > 0.05$) (Fig. 5 A). Serum glucose concentration showed a decrease in NC, CT and IT compared to Ctr ($P < 0.01$) (Fig. 5 B). The results also revealed in CT and IT groups a significant decrease in serum level of asprosin compared to NC and Ctr–Mets ($P < 0.01$, $P = 0.02$ and $P < 0.01$, $P < 0.01$ respectively) (Fig. 5 C).

4. Discussion

The aim of the present study was to determine the effects of 8-weeks continuous and interval swimming training on serum levels of asprosin and metabolic variables in rats with Mets. We demonstrated that body weight reduced 10.96% and 0.33 in IT group compared to Ctr and NC groups respectively, but no observed significant loss of body weight in CT group. We also found that 8-weeks CT and IT training was enough to decrease asporsin concentration. Asprosin acts as an orexigenic agent in the hypothalamus that is highly expressed in adipose tissue and its secretion stimulates hepatic glucose release (Duerrschmid et al., 2017). Asprosin concentration increases with fasting and decreases with refeeding, like leptin (Duerrschmid et al., 2017). One of the feature of asprosin as a newly identified adipokine is its association with insulin resistance (Alan et al., 2018). In the present study, we explored the levels of asprosin in rats with Mets compared with NC. No significant changes were observed in the asprosin levels in rats with Mets and NC in contrast with the results of Alan et al. (2018) (Alan et al., 2018). They reported an increase asprosin levels in women with polycystic ovary syndrome (PCOS) than normal control. In their study, Asprosin levels showed an independent association with insulin resistance that this results was adverse with our finding. In the current study, we did not change on the insulin resistance between groups.

The results also showed that asprosin concentration 29.50% and 33.71% decreased in CT and IT interventions groups compared to Ctr group respectively. Moreover, in contrasts to NC, serum level of asprosin reduced after 8-weeks CT (27.27%) and IT (31.62%) interventions. Even though 8-weeks of continuous and interval swimming training significantly lowered serum level of asprosin, this reduction did not differ between the groups undertaking the CT and IT exercise. Unfortunately, no reports describing the effect of CT and IT on asprosin concentration in rats with Mets; therefore analysis the current study's findings is difficult. However, Wiecek et al. (2018) (Wiecek et al., 2018) in healthy and young woman individuals showed that asprosin and irisin secretion increases and leptin secretion reduces after a single anaerobic exercise. The researchers stated that changes in the

Table 2
Metabolic syndrome indices.

	Age	BS	HDL-C	TG
SD	18 weeks	162.875 ± 22	45.125 ± 5.5	43.375 ± 16.5
HD	18 weeks	295.375 ± 48.5	31.875 ± 6	171.875 ± 19.5

SD: standard diet; HD: high-fat diet; BS: blood sugar; HDL: high-density lipoprotein cholesterol; TG: triglyceride.

Table 3
Descriptive characteristics of rats in baseline and after metabolic syndrome.

Level	Age	N	weight (g)	nose-to-anus length (cm)	Lee index	QUICKI
Baseline	6 weeks	16	275.75 ± 33	18.56 ± 1.25	301.6 ± 4.5	2.79 ± 2.16
After metabolic syndrome (before exercise)	18 weeks	32	360.53 ± 28.75	21.37 ± 0.75	333.08 ± 11.58	1.14 ± 0.98

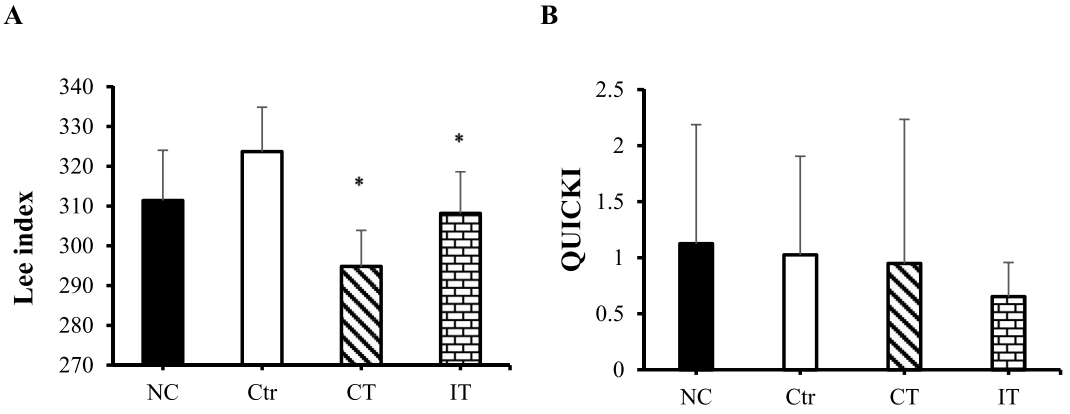

Fig. 1. (**A**) Lee index as an evaluation of obesity and (**B**) quantitative insulin-sensitivity check index (QUICKI). NC: Normal control; Ctr: control; CT: continuous training; IT: interval training. Values are means ± SD.

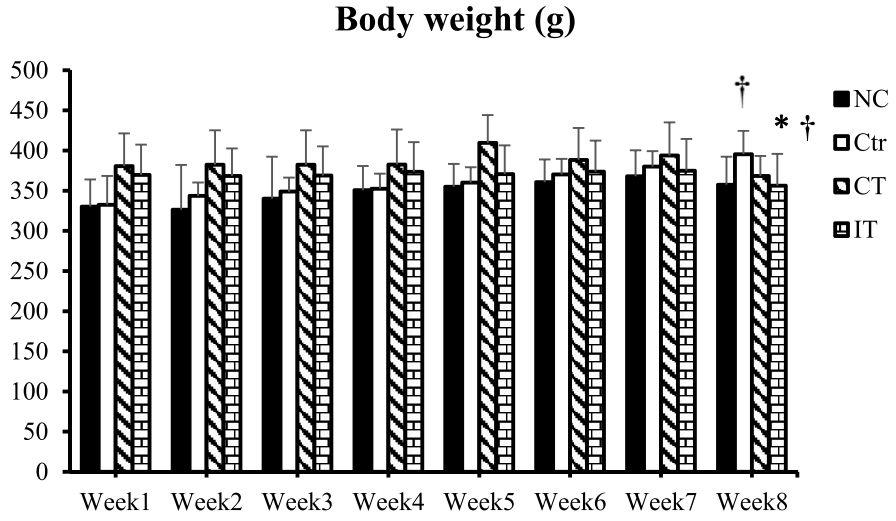

Fig. 2. Effect of continuous and interval training on rat weight (NC: Normal control; Ctr: control; CT: continuous training; IT: interval training). Rats were weighted per week. * Significant different compared to NC and Ctr $P < 0.05$; † Significant different compared to first week $P < 0.05$; Results are expressed as mean ± SD.

Table 4
Pearson Correlation coefficient of variables associated with circulating asprosin concentration.

	r	*P value*
TC	0.181	0.320
TG	0.102	0.57
HDL-C	−0.107	0.560
LDL-C	0.293	0.103
Insulin concentration	−0.209	0.250
Glucose concentration	0.515	0.003

TC: total cholesterol; TG: triglycerides; HDL: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol.

concentration of adipocytokines are inter-related. In this study, we did not investigate the other adipokine indices related to appetite that we considerate as limitation of our study.

It has been demonstrated that asprosin plays a role in the regulation of appetite (Duerrschmid et al., 2017). Asprosin is a fasting-induced glucogenic hormone (Romere et al., 2016). Circulating asprosin with crosses the blood-brain barrier and activates orexigenic $AgRP^+$ neurons via the cAMP dependent pathway, effects on the appetite (Duerrschmid et al., 2017; Wiecek et al., 2018). In addition, in the mouse model study by Duerrschmid et al. (2017) have been showed that asprosin concentration might be to decrease in obese and insulin resistant patients by neutralized antibodies, thereby lowering the activity of $AgRp^+$ neurons and resulting in a reduced daily food intake (Duerrschmid et al., 2017). In this study, we for the first time demonstrated that the serum levels of asprosin was decrease by CT and IT. Thus, it seems that both of CT and IT affecting the appetite by reduce the asprosin concentration in rats with Mets, We showed a positive correlation between asprosin and glucose concentration, in contrast individuals with normal metabolic profile (Wiecek et al., 2018). Indeed, we did not find correlation between asprosin concentration, insulin concentration and lipid profile. In adverse with our results, Zhang et al. (2017) (Zhang et al., 2017) reported that serum asprosin has a strong relationship with lipids metabolism in patients with diabetes. It has been demonstrated that

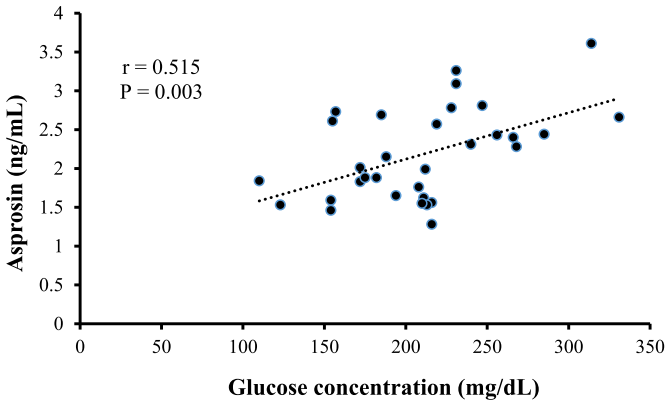

Fig. 3. Scatter plots showing the correlation of serum asprosin levels with glucose concentration.

increasing circulating asprosin concentrations in patients with T2DM might be a risk factor associated with the development of T2DM and may be involved in the pathogenesis of lipids disorder (Zhang et al., 2017).

The studies demonstrated that exercise training improves lipid profile, inflammation and adipokine production and secretion (Bachi et al., 2015; Yu et al., 2017). Here, we observed that animals in the CT and IT had improvements in serum lipid variables including, TC (25.48%, 29.07% respectively), TG (36.34%, 28.70 respectively), LDL-C (45.95%, 52.24% respectively) concentration compared to Ctr-Mets, while HDL-C and insulin concentration were not showed significant different between groups. Also, there was no significant different between trained groups. Consistent with this results, Hansen et al. (2009), showed an equally effective of continuous low and moderate-to high-intensity interval training on lipid profile in obese type 2 diabetes patients (Hansen et al., 2009). Conversely, Maiorana et al. (2002) and McGavock et al. (2004) failed to observed alterations of lipids and lipoproteins after 8–10 weeks of combined strength and aerobic training (Maiorana, O'Driscoll, Goodman, Taylor and Green, 2002; McGavock et al., 2004). The impact of exercise training on the lipid profile is variable. As describing in a previously study, the possible mechanism that explain the improvement in the lipid profile include increased muscle and adipose tissue PPARγ and PGC-1α messenger RNA expression after exercise training (Saghebjoo et al., 2018). According to our results, it seems that CT and IT exercise may present useful treatment option for prevention of progress Mets.

5. Conclusion

This is study demonstrated that CT and IT over 8-weeks were effective for controlling body weight, lipid profile and may have therapeutic preventative and protective effects on metabolic syndrome by decreasing serum levels of asprosin concentration. Based on the results of the present study it seems that low-volume exercise (~5 min) can increase similar changes when compared to continuous training (between 30 and 60 min) or even more. Further studies are required to confirm these results.

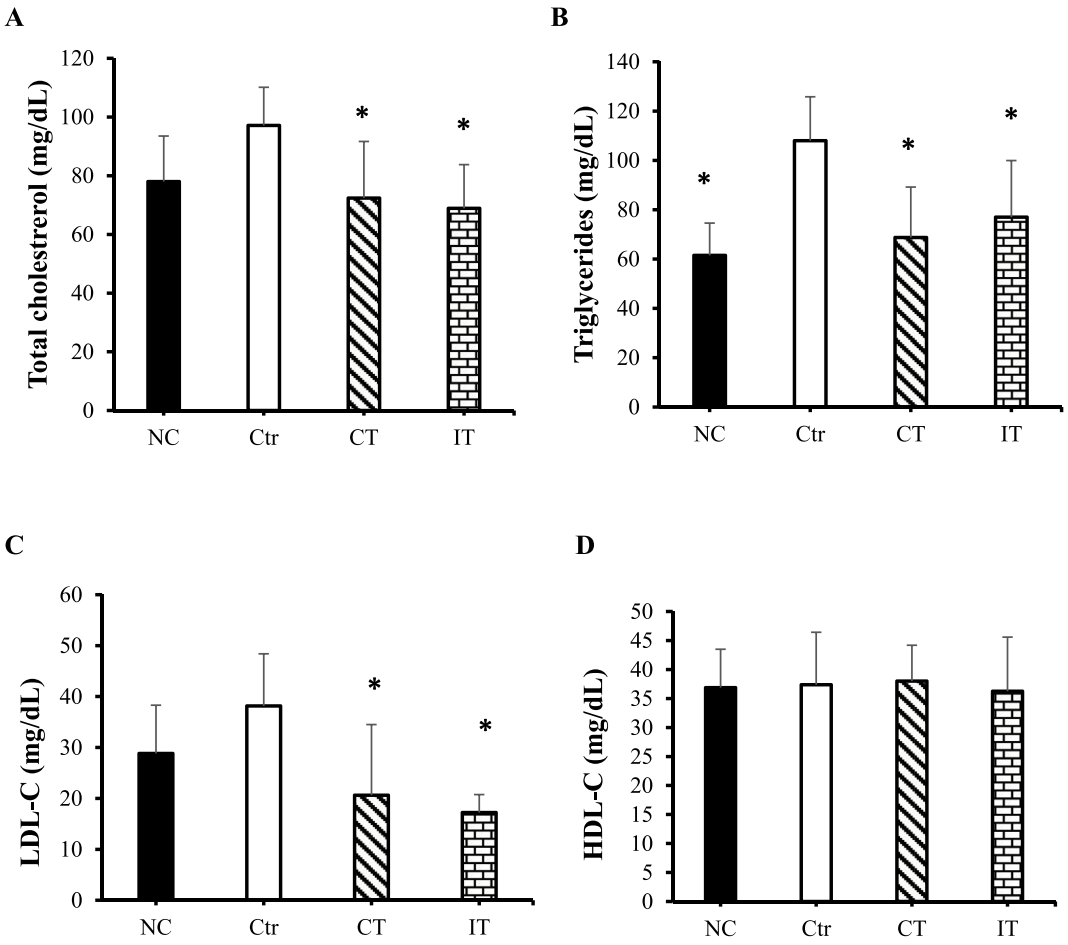

Fig. 4. Effect of interventions on serum levels of lipid profile (**A to D**). The serum levels of (**A**) total cholestrol; (**B**) triglycerides (**C**) low-intensity lipoporotein cholestrol (LDL-C) and (**D**) high-intensity lipoporotein cholestrol (HDL-C). * Significant different compared to Ctr $P < 0.05$; NC: Normal control; Ctr: control; CT: continuous training; IT: interval training. Values are means ± SD.

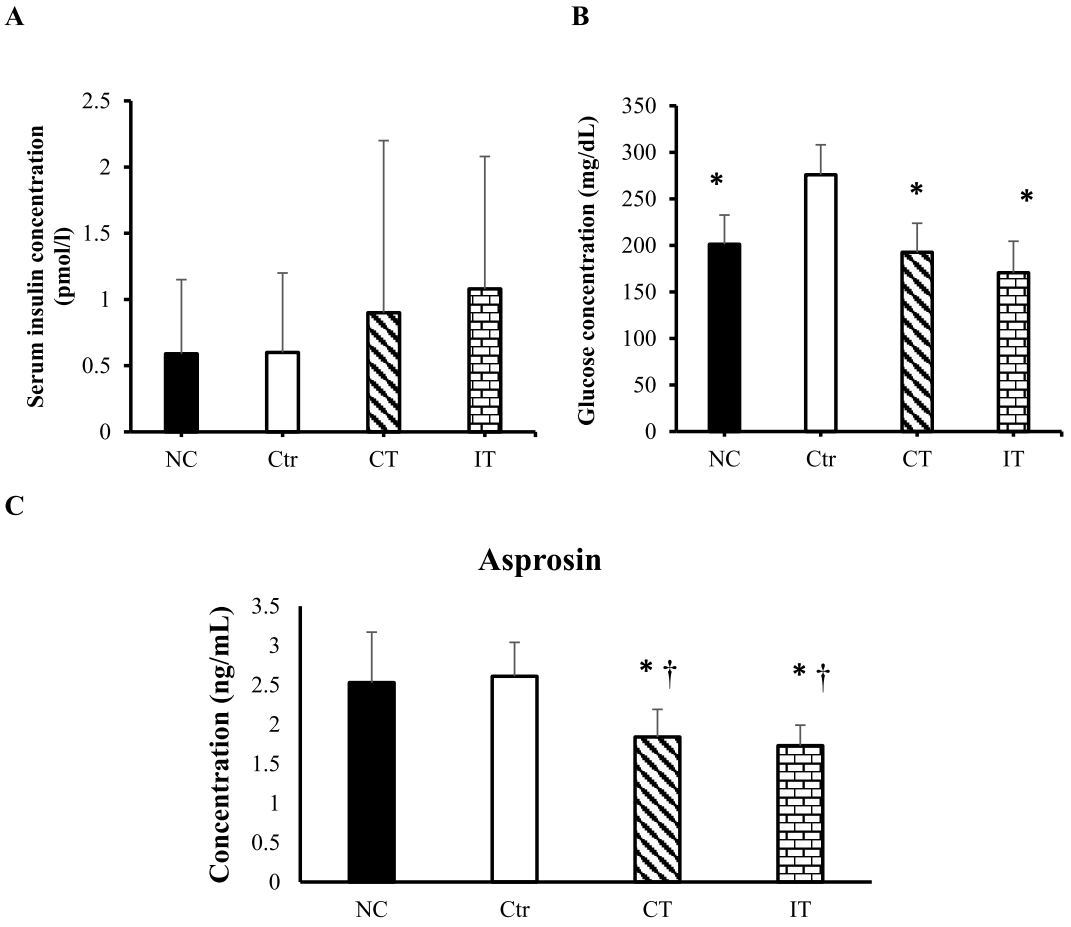

Fig. 5. Effect of interventions on serum levels of (**A**) insulin concentration; (**B**) glucose concentration (**C**) asprosin. * Significant different compared to Ctr $P < 0.05$; † Significant different compared to NC $P < 0.05$; NC: Normal control; Ctr: control; CT: continuous training; IT: interval training. Values are means ± SD.

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Declarations of interest

None.

Conflicts of interest

The authors declare that there is no duality of interest associated with this manuscript.

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