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Taurine supplementation increases irisin levels after high intensity physical training in obese women

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ABSTRACT

Background: Irisin is a myokine/adipokine that under stimulus of physical exercise is able to improve thermogenic capacity in adipose tissue. Likewise, taurine supplementation has demonstrated similar effects on energy metabolism. Therefore, we hypothesized that taurine supplementation combined with physical training may induce an increase in irisin concentrations, optimizing energy metabolism in obese individuals. *Objective:* To evaluate if taurine supplementation associated with a high intensity physical training program increases irisin levels in obese women. *Methods:* double-blind study with 22 obese women (BMI 32.4 ± 2.0 kg/m^2, 36.6 ± 6.4 years and sedentary) who were randomly divided into two groups, control group (GC, n = 14), exercised and supplemented with placebo (3 g of starch), and taurine group (GTAU, n = 8), exercised and supplemented with taurine (3 g). The subjects performed high intensity physical training, Deep Water Running (DWR), for 8 weeks, 3 times/week, for 50 min per training session, at 70–85% maximum heart rate. Resting metabolic rate (RMR) was evaluated by indirect calorimetry, body composition by deuterium oxide, plasma taurine by HPLC, plasma irisin by Multiplex Kit, and food consumption by food records. The results were analyzed by an ANOVA two way repeated measures mixed model, with the Sidak post hoc ($p < 0.05$). *Results:* No changes were observed in body composition. DWR increased RMR independent of supplementation ($p < 0.001$) and irisin levels (pg/mL) showed a significant difference only in the GTAU in 1 h after exercise ($p < 0.001$). *Conclusion*: DWR associated with taurine supplementation resulted in increased plasma irisin concentrations after physical training in obese adult women.

1. Introduction

Obesity is a chronic multifactorial disease characterized by excessive accumulation of body fat, which has reached alarming numbers worldwide [1]. Although genetic factors contribute to increased adiposity, in many cases obesity is a result of a sedentary lifestyle and high caloric intake and nutritional disorders, leading to energy imbalance and metabolic disorders [2]. Faced with this reality, different therapeutic strategies have been applied to fight obesity.

The present study investigated the effects of physical exercise associated with taurine supplementation on energy expenditure, body composition and plasma irisin levels. Several studies have demonstrated the efficacy of physical exercise in the treatment of obesity [3–6]. Among different physical training protocols, Deep Water Running (DWR) is characterized as high intensity aerobic interval training, performed in the deep part of a pool, using a flotation vest, in which the

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person stands upright with the water up to neck level and feet not touching the bottom of the pool [7,8]. The main advantage of DWR for obese individuals is elimination of impact on the lower limbs, decreasing the risk of injuries [7].

One of the most important effects of physical training is the increase in energy expenditure [6], which can decrease body fat mass [9,10]. However, the mechanism involved in these effects arises from various intermediary metabolic reactions, such as the capacity to promote thermogenic gene expression in white adipocytes ("browning" of white adipose tissue) and increase body energy expenditure [11]. One of the hypotheses is that this phenomenon is induced by a myokine called irisin. Irisin is released during exercise, derived from the cleavage of the fibronectin content domain 5 (FNDC5) [11–13]. Bostrom et al. [11] reported that one of the mechanisms related to irisin synthesis during exercise is mediated by the peroxisome proliferator-activated receptor (PGC-1alpha), receptor-1 alpha co-activator protein [14], which is involved in the control of mitochondrial biogenesis and oxidative metabolism in several cell types [15].

Furthermore, taurine (2-aminoethanesulfonic acid, Tau) is a free intracellular nitrogenous compound that has shown promising results regarding the regulation of energetic metabolism due to its ability to stimulate the production of messenger RNA for the expression of PGC-1α [2,16]. However, it has not yet been investigated whether the positive effects of the association of exercise and taurine supplementation on obesity occurs due to the increase in irisin release. Thus, the aim of the present study was to evaluate the effects of the association of DWR with taurine supplementation on body composition, energy expenditure, and plasma irisin concentration in obese women.

2. Methods

2.1. Study design and subjects

This is a randomized and double blind trial. Thirty-one obese women were recruited (BMI 32 ± 2 kg/m^2, 36 ± 6 years old). The exclusion criteria were: metabolic diseases, drug or supplement consumption, or treatment for weight loss. The study was approved by the Research Ethics Committee of the Faculty of Pharmaceutical Sciences of the State University of São Paulo/Campus of Araraquara, SP (protocol number: 51921115.5.0000.5426). All subjects gave written consent for participation. All subjects participated in evaluations before (pre) and after (post) the intervention. The intervention program had a duration of 8 weeks. The subjects were divided into two groups: Control group (GC, n = 14) and Taurine group (GTAU, n = 8). The protocol started with 31 participants, however, 9 dropped-out, 8 from the GTAU group and 1 from the GC group, due to illness and other unknown reasons, leaving the GC with 14 and GTAU with 8 participants.

2.2. Taurine or placebo supplementation

The GTAU received supplementation consisting of capsules containing 3 g of pure taurine powder (*Aminoethylsulfonic Acid*, Ajinomoto®, São Paulo, SP) [17], while the GC received a similar capsule containing starch. The supplementation was ingested 2 h before physical training (days of training) and during fasting on other days. No nutritional counseling was performed and all subjects were instructed not to consume food sources of taurine, such as energy drinks, fish, and seafood, throughout the intervention period.

2.3. Physical training

The Deep Water Running (DWR) was performed according to the protocol described by Pasetti, Gonçalves and Padovani [18]. DWR is physical training performed in the deep part of a pool wearing a flotation vest (*Actual*®, São Paulo, SP, Brazil), fixed to the waist, so the body remains submerged up to the shoulders, without the feet touching the bottom of the swimming pool. The intervention had a total duration of 10 weeks (2 weeks of adaptation and learning the movement and 8 weeks of training), with a frequency of 3 times/week for 50 min. The intensity of training was progressive, between 70 at 85% of heart rate (HR), previously determined by a performance test. The training was controlled by a frequency meter (Polar®, FT1 model) and rating of perceived exertion (RPE) according to Foster [19].

2.4. Performance test

A maximal effort test was performed for DWR according to the protocol of Wilder, Brennan and Schotte [7], which consisted of a 4-minute warm-up controlled at a cadence of 48 elevations/minute; followed by 11 stages with 2 min durations without an interval. The first stage was composed of 66 elevations/minute, and the elevations were increased by 3 in each of the next stages. All volunteers were given verbal encouragement and an evaluator monitored all cadence movements throughout the training protocol.

The heart rate (HR) and rating of perceived exertion (RPE) were recorded at the beginning and in the last 15 s of each stage, for intensity control. The test was completed when the participant could no longer maintain the rhythm of the elevations, and the HR of the previous stage was considered as the HR_{peak} for prescription of the intensity of the effort, according to the formula proposed by Karvonen, Kentala and Mustala (1957): Target HR zone = ((HR_{max} − HR $_{resting}$) * % intensity) + $HR_{resting}$.

2.5. Biochemical measurements

Blood samples were collected after 12-h of fasting in EDTA tubes and plasma was separated by centrifugation and stored at −80 °C until analysis. In addition, 4 mL of blood were collected for taurine and irisin analyses: baseline (resting), immediately post physical exercise, and 1 h after physical exercise (before and after 8 weeks of intervention).

2.6. Dietary intake

All subjects were instructed to complete a three-day food record to verify their energy intake. DietPro5i® professional software was used to examine kcal and macronutrients.

2.7. Body composition and anthropometric data

All participants were in a fasting state for evaluation. Body weight was measured using an electronic platform Fiziola TM scale with a precision of 0.1 kg and maximum capacity of 300 kg. A vertical shaft with a 0.5 cm graduation was used to measure body height. Waist circumference was measured with an inextensible tape at the largest circumference between the last rib and the iliac crest and hip circumference was measured at the maximum extension of the buttocks. Body composition was evaluated using the deuterium oxide dilution method. Each volunteer received a dose of 1 mL kg^{-1} of 7% deuterium oxide (Cambridge Isotope, Tewksbury, MA, USA). Urine samples were collected before and three hours after dose intake and samples were stored at −80 °C until analysis. Deuterium enrichments in urine samples were quantified through mass spectrometry (Europa Scientific Hydra System, Cheshire, United Kingdom) and body composition was determined as previously described [20].

2.8. Resting metabolic rate (RMR)

Indirect calorimetry with a QUARK-RMR device (COSMED, Rome, Italy) was used to determine oxygen (O_2) consumption and carbon dioxide (CO_2) production during substrate oxidation. During the evaluation, the women lay awake, in the supine position, in a quiet room at a temperature between 21 and 24 °C, under dim lighting. All the

measurements were taken between 8:00 and 10:00 am. The women were advised to fast for eight hours, not to do any physical exercise, and not to drink coffee or black tea 24 h before the assessment. The equipment was automatically calibrated with known gas concentrations before all assessments, according to the manufacturer's specifications. The volume of oxygen consumption (VO_2) and carbon dioxide production (VCO_2) were measured for 30 min. The Weir equation [21] was used to estimate RMR.

2.9. Taurine analysis

Plasma taurine was quantified by high-performance liquid chromatography (Shimadzu, model LC 10AD) through the method of Deyl et al. [22]. Taurine 99% (Sigma-Aldrich, St. Louis, MO, USA) was used as a standard.

2.10. Irisin analysis

Plasma irisin was assessed by Multiplex (Merck Millipore®, Kenilworth, Nova Jersey, USA), using "*Human Myokine Magnetic Bead Panel*" (Saint. Charles, USA), monoclonal (HMYOMAG-56 K) panels. No cross-reactions were detected and the values were expressed as pg/mL. The sensitivity of the irisin kit was 0.02 pg/mL – 3000 pg/mL with a range of 244 pg/mL − 1000.000 pg/mL.

2.11. Statistical analysis

Descriptive statistics consisted of mean values and standard deviation. Data normality was verified by the Shapiro-Wilk test. For the characterization of the subjects, a non-paired Student *t*-test was performed. The sphericity was validated by an ANOVA two way repeated measures mixed model, followed by the post-hoc (Sidak) in cases of group*time interaction (*software* SPSS *Statistics* 20®, Armonk, NY, US). For interpretation of the results, the Eta squared (η^2) was used as a measure of the effect size in ANOVA, according to the formula: η^2 = SSeffect/SStotal, where SSeffect is the sum of the squares for any effect of interest and SStotal is the sum total (sum of the SSeffect) for all effects, interactions, and errors [23]. The Eta squared can be interpreted according to the scale of η^2: 0.1–0.29 (small), 0.3–0.49 (moderate), and ≥0.5 (high). A significance level of 5% was adopted.

3. Results

General characteristics of participants were presented in Table 1 and it was observed that the groups were similar at the start of the intervention, except for age and waist circumference.

After 8 weeks of intervention with DWR associated with taurine or placebo supplementation, there were no observed changes in body weight, BMI, waist and hip circumference, or body composition. However, the RMR increased ($p < 0.001$) after 8 weeks of physical training, independent of the supplementation protocol, and showed a high magnitude of effect ($\eta^2 = 0.5$) (Table 2).

Regarding the physical fitness variables, the participants presented, on average, an HRpeak of 171 ± 11.5 bpm (pre) and 174 ± 1.38 bpm (post) and $HR_{resting}$ of 80 ± 8.64 bpm (pre) and 86 ± 9, 75 bpm (post). In addition, the total time performed in the maximal effort test was higher after 8 weeks of physical training, independent of the supplementation protocol ($p < 0.011$), indicating an improvement in aerobic capacity.

In relation to the nutritional assessment, a significant decrease in total caloric intake was observed only for the GC ($p = 0.03$), whereas the protein intake in the GTAU was significantly higher after the 8 weeks intervention ($p = 0.006$) (Table 3). The ingestion of lipids and carbohydrates was similar when comparing pre and post intervention.

Plasma levels of taurine were significantly higher after 8 weeks of intervention for the GTAU baseline (pre 14.70 ± 3.93 μmol/L and post 113.10 ± 56.85 μmol/L ($p < 0.001$, ~7.7 fold) and 1 h after exercise (pre 14.18 ± 3.34 μmol/L and post 70.87 ± 44.30 μmol/L) ($p < 0.001$, ~5 fold).

Table 1
General characteristics of participants at baseline.

	GC (n = 14)	GTAU (n = 8)	p value
Age (years)	38.9 ± 4.7	32.7 ± 7.3	0.026*
Weight (kg)	89.0 ± 9.8	88.8 ± 6.7	0.952
BMI (kg/m^2)	32.8 ± 2.2	32.0 ± 1.7	0.365
WC (cm)	110.2 ± 8.0	104.3 ± 4.4	0.039*
HC (cm)	117.9 ± 7.4	118.2 ± 3.0	0.897
Body fat (%)	49.8 ± 6.8	46.6 ± 5.9	0.284
Fat-free mass (%)	50.1 ± 6.8	53.3 ± 5.9	0.268
RMR (kcal/day)	1519.4 ± 168.7	1606.2 ± 139.9	0.233
Cholesterol (mg/dL)	217.9 ± 34.6	224.1 ± 34.5	0.693
LDL-C (mg/dL)	154.4 ± 29.4	152.9 ± 42.8	0.920
HDL-C (mg/dL)	40.6 ± 14.1	52.9 ± 23.4	0.138
TG (mg/dL)	114.2 ± 38.6	91.6 ± 21.1	0.143
Energy (kcal)	2062 ± 690.1	1703 ± 665.7	0.270
Protein (%)	19.4 ± 4.4	20.7 ± 5.2	0.544
Lipids (%)	32.8 ± 5.9	31.9 ± 6.6	0.757
Carbohydrate (%)	47.6 ± 8.7	47.4 ± 10.9	0.963
Taurine (μmol/L)	16.97 ± 2.06	14.70 ± 3.93	0.088

BMI: Body Mass Index, **WC**: waist circumference, **HC**: hip circumference, **RMR**: Resting metabolic rate. **GC**: control group, **GTAU**: taurine group. **LDL-C**: Low-density lipoprotein cholesterol; **HDL-C**: High-density lipoprotein cholesterol; **TG**: Triglycerides. Values expressed as mean ± standard deviation. *Differences between groups ($p < 0.05$) by no-paired Student *t*-test.

The results of plasma irisin levels are described in Fig. 1. It was observed that 1 h post exercise the irisin levels were increased in the GTAU ($p < 0.001$), when compared to the GC, after 8 weeks of intervention. On the other hand, when analyzing the different evaluation moments post intervention in the GC, higher levels of irisin were observed at baseline when compared to immediately after exercise ($p = 0.017$) and 1 h post exercise ($p = 0.001$). Furthermore, it is important to emphasize the high magnitude of effect for irisin levels in the GTAU group in the 1 h post exercise evaluation, after the 8 week intervention ($\eta^2 = 0.6$).

4. Discussion

The main findings of the present study were: (a) 8 weeks of DWR training increased RMR in both experimental groups; (b) taurine supplementation associated with physical training promoted higher plasma concentrations of irisin.

Nevertheless, DWR training and taurine supplementation did not cause weight loss or changes in body composition, different from other studies that showed changes in body composition after 12 or 16 weeks of high intensity aerobic training [18,24]. This absence could be related to insufficient time of the training or lack of a food intervention, although subjects were requested to maintain their food pattern intake along the intervention. However, reductions in energy consumption and changes in diet composition are necessary for the weight loss process [25].

Our results clearly showed that the increases in resting energy expenditure after physical training, independent of increases in fat free mass. Energy expenditure induced by physical training is variable in subjects and could be an opportunity to enhance resting energy expenditure, which could favor body weight control [26–28].

Physical exercise is also important to influence changes in habitual diet [29]. However, only GTAU group presented changes in food intake, which were related to an increase in protein intake. It is important to report that no nutritional counseling was performed and the participants were free to their food choices, and the supplementation was not related to food intake. Thus, the changes observed may have occurred due to the influence of exercise on achieving a healthy way of life [29].

Table 2
Anthropometric measures, body composition and resting metabolic rate before and after the intervention.

	GC (n = 14)			GTAU (n = 8)			
Variable	pre	post	Δ%	Pre	post	Δ%	p value
Weight (Kg)	89.0 ± 9.8	88.3 ± 9.4	0.8	88.8 ± 6.7	88.2 ± 7.0	1.7	0.175
BMI (Kg/m^2)	32.8 ± 2.2	32.6 ± 1.9	0.6	32.0 ± 1.7	31.8 ± 2.1	0.6	0.364
WC (cm)	110.2 ± 8.0	109.0 ± 6.8	1.1	104.3 ± 4.4	106.6 ± 4.6	2.2	0.561
HC (cm)	117.9 ± 7.4	117.3 ± 6.9	0.5	118.2 ± 3.0	116.9 ± 3.4	1.1	0.250
Body fat (%)	49.8 ± 6.8	51.2 ± 4.2	2.8	46.6 ± 5.9	47.2 ± 6.5	1.2	0.382
Fat-free mass (%)	50.1 ± 6.8	48.7 ± 4.2	−2.8	53.3 ± 5.9	52.7 ± 6.5	−1.1	0.382
RMR (kcal/day)	1519.4 ± 168.7	1667.8 ± 164.5	9.7	1606.2 ± 139.9	1703.3 ± 158.5	6.0	<0.001*

BMI: Body Mass Index, **WC**: waist circumference, **HC**: hip circumference, **RMR**: Resting metabolic rate. **GC**: control group, **GTAU**: taurine group. Δ%, variation between pre and post of each group. Values expressed as mean ± standard deviation. *Pre and post difference ($p < 0.05$) independent of groups by ANOVA two-way repeated measures mixed model. RMR: $\eta^2 = 0.5$.

Moreover, there are few studies describing main food protein which contains taurine [30–32]. Due to the low levels of taurine in meats and dairy products [32] and non detectable levels in vegetables and nuts [31], we believe that the increase in protein intake observed did not have influenced taurine blood levels.

In addition, although there were no changes in total energy intake, it is rather low regarding that the participants were overweight. This fact can be related to the difficult to obtain reliable dietary records from obese individuals because of food intake underreporting [33].

Regarding plasma irisin concentrations, previous studies with humans have investigated the possible associations between diet and irisin release and showed that the food intake does not changes the circulating levels of irisin [34–36].

Park et al. [35] and Anastasilakis et al. [36] evaluated the relationship between irisin and dietary intake and concluded that irisin release is not associated with the diet quality, total energy intake or dietary macronutrients content. Therefore, the increase in irisin levels observed in the present study can be attributed to physical exercise, since that irisin is a myokine released in response to exercise [12,37–39]. Furthermore, irisin is also considered an adipokine and it is released in the adipose tissue mediated by exercise, it regulates energy metabolism and can promote thermogenesis or "beiging/browning" of white adipose tissue [11,40].

Studies have shown that aerobic and interval exercises, acute or chronic [40–42], increase FNDC5/Irisin expression. A crossover investigation developed by Huh et al. [39] with subjects with or without metabolic syndrome compared the effects of three exercise protocols on irisin release before, immediately after and one hour post exercise. The authors observed that all protocols increased irisin levels immediately after, but a decrease was observed one hour post exercise.

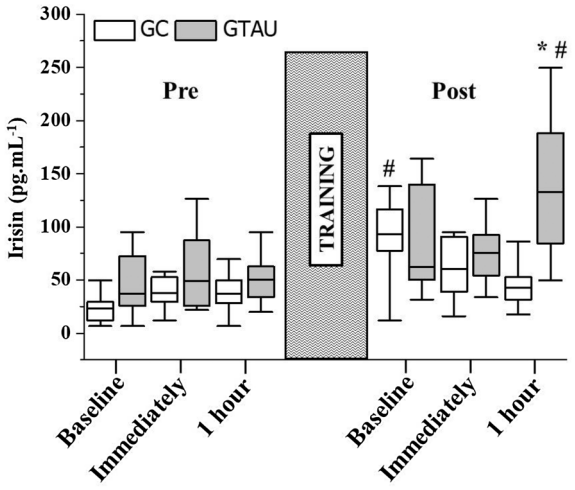

Fig. 1. Plasma irisin levels (pg/mL) represented by boxplot. **GC:** control group (n = 13, because one of the samples was not detected in the irisin assay), **GTAU**: taurine group (n = 8), **Baseline**: rest without exercise, **Immediately**: immediately after exercise, **1 h**: 1 h after exercise. * Difference between groups at 1 h after 8 weeks training ($p < 0.001$), interaction group*time. # Difference within the group in post intervention: GC baseline vs immediately ($p = 0.017$), baseline vs 1 h ($p = 0.001$); GTAU 1 h vs baseline ($p = 0.008$), 1 h vs immediately ($p = 0.004$), by ANOVA two-way repeated measures mixed model, post hoc Sidak.

Controversially to Huh et al [39], the present study showed that the combination of physical training with taurine supplementation was able to potentiate the effects of exercise on irisin release because it

Table 3
Food consumption before and after intervention.

	GC (n = 14)		GTAU (n = 8)		
Macronutrients	pre	post	pre	post	p value
Energy (kcal)	2062 ± 690.1	1671 ± 445.5	1703 ± 665.7	1523 ± 435.2	ES: 0.25 EE: 0.03* INT: 0.68
Protein (%)	19.4 ± 4.4	19.0 ± 3.3	20.7 ± 5.2	22.9 ± 4.1	ES: 0.006* EE:0.792 INT: 0.21
Lipids (%)	32.8 ± 5.9	32.2 ± 4.2	31.9 ± 6.6	31.2 ± 6.0	ES:0.891 EE:0.759 INT:0.77
Carbohydrate (%)	47.6 ± 8.7	48.8 ± 6.6	47.4 ± 10.9	45.8 ± 6.9	ES:0.364 EE:0.665 INT: 0.32

Values expressed as mean ± standard deviation. *pre and post difference by ANOVA two-way repeated measures mixed model post hoc Sidak ($p < 0.05$). **GC**: control group, **GTAU**: taurine group, **ES**: effect of supplementation, **EE**: exercise effect, **INT**: interaction.

promoted a greater permanence of this cytokine.

We found enhanced plasma irisin concentrations after 8 weeks of training. Furthermore, positive modulations in irisin concentrations were observed with taurine supplementation associated with physical training, demonstrated by the high effect size in the GTAU ($\eta^2 = 0.53$). This result suggests that, possibly, the taurine and irisin molecules may be dynamically influenced by one another via the energy metabolism pathway. Irisin synthesis from an increase in PGC1-α expression through physical exercise promoted thermogenesis processes and increased energy expenditure [11].

In addition, taurine supplementation increased oxygen consumption, mRNA levels of transcriptional factors, and cofactors involved in energy expenditure (receptors activated by peroxisome proliferator - alpha and gamma - PPAR-alpha and gamma), and PGC1-alpha in rodents [16]. Furthermore, taurine is also able of stimulating the expression of important decoupling proteins involved in the mitochondrial respiration process, promoting an increase in energy expenditure [2]. Additional investigations are necessary to clarify possible mechanisms involved in the synergistic action between irisin and taurine associated to exercise in humans.

It is important to point out limitations of the study. No nutritional counseling intervention was performed, however the participants were instructed to not consume foods that were source of taurine. A controlled diet could have been more accurate to manage the total calories and macronutrient intake, nevertheless the purpose of the study was not to make a nutritional intervention, but only to investigate the effects of the supplementation taurine associated to exercise. Additionally, the 8-week intervention period proposed was not enough for promoting body composition changes. From this, it is clear the importance of nutritional intervention and physical training to promote weight loss and obesity management.

Finally, we hightlight the strength points of the present investigation: it is the first study that investigated the association between taurine supplementation and physical training effects on irisin release in obese women. Considering that taurine supplementation could modulate energy metabolism and that irisin plays a role-key as a metabolic regulator in response to physical training, the combined action of the nutrient with myokine can improve the crosstalk between skeletal muscle and adipose tissue, being an important strategy for obesity treatment.

5. Conclusion

It was concluded that taurine supplementation, when associated with physical training, may be a viable strategy to elevate irisin levels in obesity conditions. Furthermore, DWR resulted in higher resting metabolic rate, which also provides benefits for obese individuals.

Declaration of Competing Interest

None of the authors declare competing financial interests.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cyto.2019.154741.

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