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ORIGINAL CONTRIBUTION

Oxidative stress and inflammation in obesity after taurine supplementation: a double-blind, placebo-controlled study

Flávia Troncon Rosa · Ellen Cristini Freitas · Rafael Deminice · Alceu Afonso Jordão · Julio Sérgio Marchini

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Abstract
Purpose Some researchers found decreased levels of plasma taurine in obese subjects and animals, and reduced expression of an important enzyme of taurine synthesis. These evidences, coupled with the metabolic imbalance of obesity and the possible anti-inflammatory and antioxidant effects of taurine, highlighted the use of taurine as a supplement in obesity treatment. The aim of the present study was to investigate whether taurine supplementation, associated with nutritional counseling, modulates oxidative stress, inflammatory response, and glucose homeostasis in obese women.
Methods A randomized double-blind placebo-controlled study was conducted with 16 women with obesity diagnosis and 8 women in the normal weight range. The obese volunteers were matched by age and body mass index and randomly assigned to either the placebo (3 g/day starch flour) or taurine (3 g/day taurine) group. The study lasted 8 weeks, and the experimental protocol included nutritional assessment and determination of plasma sulfur amino acids, insulin, and adiponectin, serum glycemia, and markers of inflammatory response and oxidative stress.
Results Plasma taurine levels were significantly decreased (41 %) in the obese volunteers. Both the placebo and taurine groups showed significant reduction in weight (3 %), with no differences between groups. Different from placebo, taurine-supplemented group showed significant increase in plasma taurine (97 %) and adiponectin (12 %) and significant reduction in the inflammatory marker hs-C-reactive protein (29 %) and in the lipid peroxidation marker thiobarbituric acid reactive substances (TBARS) (20 %).
Conclusions Eight weeks of taurine supplementation associated with nutritional counseling is able to increase adiponectin levels and to decrease markers of inflammation (high-sensitivity C-reactive protein) and lipid peroxidation (TBARS) in obese women.

Keywords Taurine · Obesity · Inflammation · Oxidative stress · Adiponectin

Introduction

Characterized by excessive accumulation of body fat, obesity is a multifactorial chronic disease of increasing prevalence both in developed and developing countries. Worldwide, more than 1 billion adults are above their ideal weight for height, sex, and age, with about 500 million having a diagnosis of obesity [1].

Evidence of oxidative stress induced by obesity has been demonstrated by increased levels of lipid peroxidation markers, as well as reduced antioxidants such as glutathione (GSH) levels and superoxide dismutase and glutathione peroxidase enzymes. The mechanism underlying oxidative stress in obesity is multifactorial, including

F. T. Rosa (✉) · A. A. Jordão · J. S. Marchini
Department of Internal Medicine, Faculty of Medicine of Ribeirão Preto, University of São Paulo, Avenida Bandeirantes, 3900, Monte Alegre, Ribeirão Preto, SP CEP 14049-900, Brazil
e-mail: flaviatrosa@yahoo.com.br

E. C. Freitas
School of Physical Education and Sports of Ribeirão Preto, University of São Paulo, Avenida Bandeirantes, 3900, Monte Alegre, Ribeirão Preto, SP CEP 14040-907, Brazil

R. Deminice
Institute of Physical Education and Sport, State University of Londrina, Rodovia Celso Garcia Cid, Pr 445 Km 380, Campus Universitário, Londrina, PR CEP 86051-980, Brazil

hyperglycemia, increased oxygen consumption, and cell respiration rate; increased tissue levels of lipids and free fatty acids; inadequate antioxidant defense system, and chronic inflammation [2]. The low-grade chronic inflammation associated with obesity is evident in many tissues such as adipose tissue, liver, pancreas, skeletal muscle, and brain. The obesity-related oxidative stress and inflammation have been also associated with insulin resistance. Inflammatory mediators activate enzyme complexes that promote phosphorylation of serine residues in the insulin receptor substrate-1 instead of tyrosine residues and inhibit insulin signaling cascade [3].

Taurine (2-aminoethanesulfonic acid, Tau) is a sulfur amino acid synthesized endogenously from cysteine (Cys) or via conversion from methionine (Met), but also provided by diet, especially fish and seafood. The main pathway of Tau synthesis in mammalian involves the oxidation of L-cysteine by the cysteine dioxygenase (CDO) to produce cysteine sulfinic acid. This acid is decarboxylated to hypotaurine by the cysteine sulfinic acid decarboxylase, which is finally oxidized to taurine by hypotaurine dehydrogenase [4, 5]. Taurine derived from the diet circulates in modest amounts in plasma for transport to other tissues [4]. Plasma concentration is diet-dependent and regulated by the kidney [4]. Researchers found that gastrointestinal absorption of 4 g taurine occurs 1–2.5 h following oral administration, and plasma levels returns to endogenous concentrations after 6–8 h [6]. Reduced plasma taurine levels were observed in obese patients [7] and in high-fat diet-induced or genetically obese mice [8].

Although Tau has been studied for decades, especially because of its effects on bile acids conjugation and retina development [7], the role of Tau supplementation has been extended to its function as anti-inflammatory [9, 10] and antioxidant agent [11–14]. Tau supplementation has also improved insulin sensitivity and normalized glycemia in animal models of obesity [15–17] and in overweight and obese men [13]. However, to the best of our knowledge, no study has directly investigated the effects of Tau supplementation on metabolic disorders such as oxidative stress and inflammation in obese women. Thus, the aim of the present study was to investigate whether Tau supplementation, associated with nutritional counseling, modulates oxidative stress, inflammatory response, and glucose homeostasis in obese women.

Subjects and methods

Subjects

Sixteen women with obesity diagnosis according to body mass index (BMI) and eight women in the normal weight range were recruited to the study. Exclusion criteria were as follows: diagnosis of diabetes, thyroid, liver, or kidney disorders; smoking; use of anti-inflammatory drugs, corticosteroids, or antibiotics; use of medications that alter metabolism or body composition; <20 years or more than 45 years. The volunteers were sedentary and were instructed not to change their daily activity during the course of the study.

The Ethics Committee of the University Hospital of the Faculty of Medicine of Ribeirão Preto approved the study. All subjects gave written informed consent to participate after the purpose of the study and the risks involved had been explained.

Study design

A randomized, double-blind, placebo-controlled study was conducted at the University Hospital of the Faculty of Medicine of Ribeirão Preto, University of São Paulo, Brazil. The volunteers were matched by age and BMI and randomly assigned to either placebo ($n = 8$) or taurine-supplemented obese group ($n = 8$). A third normal weight range group ($n = 8$) was recruited as a control, mainly, for taurine nutritional status evaluation. The taurine group received 3 g of taurine per day [18], and the placebo group received 3 g of starch flour, which was identical in appearance to taurine capsules. The taurine was obtained from Ajinomoto (Ajinomoto CO., INC., Limeira, SP, Brazil), and the capsules were produced at the pharmacy of the University Hospital. The study lasted 8 weeks, with weekly meetings in a Nutritional Counseling Group Program to a closer monitoring of food intake and weight loss. The experimental protocol was applied at baseline and after 8 weeks of supplementation and included nutritional assessment and blood collection for determination of plasma taurine, insulin and adiponectin, serum glycemia, and markers of inflammatory response and oxidative stress. The volunteers were instructed to take the capsules twice a day between meals and to fast for 12 h prior to blood collection.

Nutritional assessment

Anthropometry was based on the measurement of weight, height, and BMI. A 3-day food record was applied to assess food intake. The records were filled by the volunteers on 2 weekdays and 1 weekend day. The software DietPro 5.1 (A.S. Sistemas, Viçosa, MG, Brazil) was used to quantify the mean intake of macronutrients and energy.

Blood assays

Serum glucose was determined by the glucose oxidase method using a commercially available kit (LABTEST®;

Labtest Diagnóstica, Lagoa Santa, MG, Brazil). Plasma insulin, leptin, interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) were determined by LUMINEX® xMAP® technique (Luminex Corporation, Austin, TX, USA) using the human metabolic panel Multiplex MILLIPLEX® xMAP® HMH-34 K (Millipore Company, Billerica, MA, USA). Insulin resistance was determined by homeostasis model assessment of insulin resistance (HOMA-IR) calculated by the following formula: HOMA-IR = [(fasting glycemia (mg/dL) × 0.05551) × fasting insulin (μU/mL)]/22.5. Plasma high molecular weight adiponectin was determined by ELISA using the commercially available kit Human HMW Adiponectin EZ-HMWA-64 K (Millipore Company, Billerica, MA, USA). High-sensitivity C-reactive protein (hs-CRP) was quantified by immunoturbidimetry method using a commercially available kit (LABTEST®; Labtest Diagnóstica, Lagoa Santa, MG, Brasil).

Plasma-reduced GSH levels and the ferric-reducing antioxidant power (FRAP) were determined as antioxidant markers by the methods described by Costa et al. [19] and Benzie and Strain [20], respectively, using a UV–Vis Spectramax M5® microplate reader (Molecular Device, USA). Plasma vitamin E (α-tocopherol) concentration was determined by the method described by Jordão et al. [21] using an HPLC with a UV/Vis detector (Shimadzu, Kyoto, Japan). Thiobarbituric acid reactive substances (TBARS) were assessed as plasma lipid peroxidation biomarkers according to method described by Costa et al. [19], and the advanced oxidation protein products (AOPP) were based on the method described by Witko-Sarsat et al. [22]. Readings were taken using a UV–Vis Spectramax M5® microplate reader (Molecular Device, USA).

Amino acids assay

Plasma Tau was determined by high-performance liquid chromatography (Shimadzu®, model LC 10AD) using a Shimadzu model RF 535 fluorescence detector. Taurine ≥99 % was used as standard (Sigma-Aldrich®, St. Louis, MO, USA) [23]. Concentrations of the sulfur-containing free amino acids cysteine, methionine, and homocysteine (Hcy) in plasma were determined by gas chromatography (BF-17A FID Shimadzu®, Kyoto, Japan) by amino acid derivatization using an EZ:Faast Free kit (Physiological) for amino acid analysis (Phenomenex®).

Nutritional counseling group program

The program consisted of weekly meetings of 1-h long to discuss topics related to nutrition and quality of life. The diet was planned on an individual basis according to the resting energy expenditure of each volunteer, measured by indirect calorimetry. The composition of the diet followed the acceptable macronutrient distribution ranges (20–35 % total fat, 45–65 % carbohydrate, and 10–35 % protein) [24].

Statistical analysis

A linear mixed model was used to determine differences between groups (placebo and taurine) and times (basal and 8 weeks). The subjects were considered as random effects and time and intervention as fixed effects. The model was fitted using the PROC MIXED feature of the SAS software, version 9.2 (SAS Institute, Cary, NC, USA). The *t* test for independent samples was applied to determine the differences between the normal weight and the obese groups. The SPSS software version 15.0 was used for these tests. Data are reported as mean ± standard error, and the level of significance was set at 5 % ($p < 0.05$).

Results

Table 1 presents clinical characteristics of the obese volunteers compared to the normal weight control group. Plasma Tau levels were significantly decreased (41 %), and TBARS were increased (29 %) in the obese volunteers. The obese group had normal fasting glycemia (<100 mg/dL), but increased insulin levels. On the basis of HOMA-IR index, the volunteers had a diagnosis of insulin resistance (values >3.9 mol μU/L). Obese woman had increased HOMA-IR and hs-CRP values as well as decreased adiponectin levels compared to control.

There were no differences between the placebo- and taurine-supplemented groups regarding age, weight, and BMI at the beginning of the intervention. Both placebo and taurine groups showed significant reduction in weight (3 %) at the end of the intervention, with no significant difference between groups (Table 2). Energy intake was significantly reduced after 8 weeks of nutritional counseling, with no difference between groups. Although the reduction in quantities, the eating pattern of macronutrients (% of energy) remained unchanged between groups.

Figure 1 presents the plasma concentration of Tau in placebo and taurine groups at baseline and after 8 weeks of supplementation. There was no difference in basal concentrations between groups. Eight weeks of taurine supplementation significantly increased taurine plasma levels (97 %).

Concentrations of sulfur amino acids and oxidative stress markers are presented in Table 3. A significant reduction in TBARS (20 %) was observed after 8 weeks of Tau supplementation compared to their respective baseline levels. Cys, Met, Hcy, GSH, AOPP, and FRAP did not

Table 1 Baseline clinical characteristics of the obese group compared to the normal weight control group

	Obese ($n = 16$)		Normal weight control ($n = 8$)	
	Mean	SEM	Mean	SEM
Anthropometry				
Age (years)	32	2	33	4
Weight (kg)	123[a]	4	60[b]	3
BMI (kg/m^2)	47.0[a]	1.5	21.0[b]	0.5
Metabolic profile				
Glycemia (mg/dL)	89	2	78	9
Insulin (mU/L)	21.0[a]	2.3	4.1[b]	1.7
HOMA-IR	4.7[a]	0.6	0.7[b]	0.3
HMW adiponectin (μg/mL)	3.1[a]	0.6	6.1[b]	0.7
hs-CRP (mg/L)	13.3[a]	1.8	0.4[b]	0.2
Sulfur amino acids				
Taurine (μmol/L)	59[a]	4	100[b]	8
Cysteine (μmol/L)	277	12	271	9
Methionine (μmol/L)	27	2	24	2
Homocysteine (μmol/L)	6.2	0.8	5.6	0.6
Oxidative stress markers				
TBARS (μmol/L)	22.0[a]	1.5	17.0[b]	1.0
AOPP (μmol/L)	173	21	121	19
FRAP (μmol/L)	985	76	885	24
GSH (μmol/L)	441	31	430	40
α-Tocopherol (μmol/L)	15.0	1.0	14.0	0.7

SEM standard error of the mean, *BMI* body mass index, *HOMA-IR* homeostatic model assessment of insulin resistance, *HMW* adiponectin, high molecular weight adiponectin, *hs-CRP* high-sensitivity C-reactive protein, *TBARS* thiobarbituric acid reactive species, *AOPP* advanced oxidation protein products, *FRAP* ferric-reducing antioxidant power, *GSH* reduced glutathione. Different letters mean significant difference between groups ($p < 0.05$, independent samples *t* test)

change after placebo or taurine supplementation. Reductions in glycemia, insulin, and HOMA index were observed only after 8 weeks of taurine supplementation, but did not reach statistical significance. In addition, taurine supplementation was able to increase adiponectin levels (12 %) what was not evidenced in the placebo group (Table 3).

Regarding inflammation markers, it was found a significant reduction on hs-CRP (29 %) after 8 weeks in Tau supplementation, with no changes in placebo group. Concentrations of IL-6 and TNF-α did not change after the intervention (Fig. 2).

Discussion

The present study was designed to investigate the effects of Tau supplementation in obese women. The most important results of the present study were that Tau supplementation associated with nutritional counseling was able to increase adiponectin levels and to decrease markers of inflammation (hs-CRP) and lipid peroxidation (TBARS) after 8 weeks of intervention. The inclusion of a Nutritional Counseling Group Program was implemented to a better food intake control due to controversy studies that investigate single nutrients, or compounds, to treat obesity and related disorders [25] without considering changes in food intake.

The initial characterization of the obese volunteers showed increased levels of insulin, HOMA index, TBARS, and hs-CRP and decreased levels of adiponectin compared to normal weight women. As previously demonstrated by Jeevanandam et al. [7], the obese volunteers of the present study had significantly reduced plasma Tau levels. Although endogenous synthesis of Tau depends on the availability of cysteine and methionine, the concentrations

Table 2 Obese women anthropometry and food intake after 8 weeks of placebo or taurine supplementation

	Placebo ($n = 8$)				Taurine ($n = 8$)			
	Basal		8 weeks		Basal		8 weeks	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
Anthropometry								
Weight (kg)	121[a]	4	117[b]	4	125[a]	7	121[b]	6
BMI (kg/m^2)	47[a]	2	45[b]	2	47[a]	2	45[b]	2
Food intake								
Energy (kcal/day)	1,976[a]	117	1,434[b]	106	2,458[a]	295	1,852[b]	192
Proteins (% of energy)	18	1	20	2	18	1	23	2
Carbohydrates (% of energy)	51	2	48	3	49	2	47	2
Fats (% of energy)	31	2	32	3	33	2	31	2
Fibers (g)	13	2	13	1	14	2	13	1

SEM standard error of the mean, *BMI* body mass index. Different letters mean significant difference within or between groups ($p < 0.05$; linear mixed model)

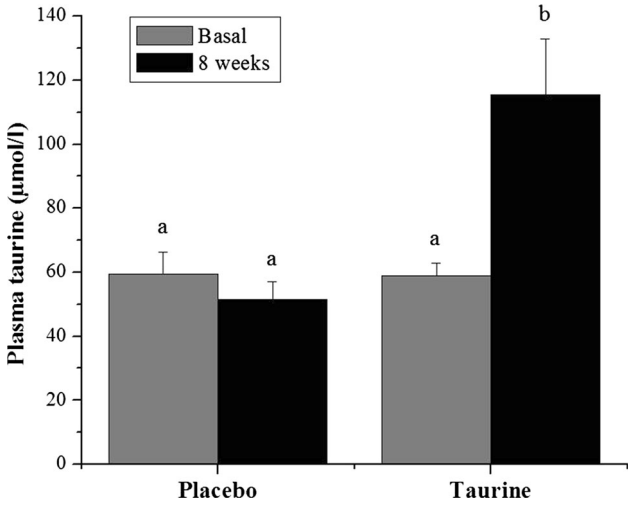

Fig. 1 Obese women plasma taurine concentration after 8 weeks of taurine or placebo supplementation. Data are reported as mean and standard error. *Different letters* means significant difference within or between groups ($p < 0.05$; linear mixed model)

of the sulfur-containing amino acids did not differ between the obese and normal weight groups. The cause of low Tau levels in obese subjects is still unknown; however, animal studies demonstrated reduction of the CDO enzyme expression in white adipose tissue of genetically or high-fat diet-induced obese mice [8].

The increased TBARS levels significantly reduced after 8 weeks of taurine supplementation, with maintenance of GSH levels. Tau has proved to be a protective factor against oxidative tissue injury in animal models. Study conducted on rabbits fed a cholesterol-rich diet demonstrated that the taurine-supplemented group showed lower increase in plasma, liver, and aorta malondialdehyde levels, with no changes on hepatic GSH levels or SOD activity [12]. Similar results were found in rats fed oxidized fish oil [11] and in iron-overloaded mice [26] after Tau supplementation. Although several animal studies have shown beneficial effect of Tau on oxidative stress induced by different agents, studies demonstrating such effects in humans are scarce. Zhang et al. [27] supplemented male students with 6 g Tau per day for 7 days in order to test its effect on the prevention of injury induced by exhaustive exercise. The authors found significant reduction in serum TBARS at baseline, with no changes after 6 h of exercise. Xiao et al. [13] demonstrated that 3 g/day Tau supplementation for 2 weeks to nondiabetic overweight or obese men prevented the increase in plasma malondialdehyde induced by a 48 h-intravenous lipid infusion.

The mechanisms by which Tau acts as an antioxidant have not been clearly defined. Some studies suggested its ability to sequester reactive oxygen species [13], or to restore antioxidant enzymes activity and regenerate thiol

Table 3 Obese women concentrations of sulfur amino acids, markers of oxidative stress and glucose metabolism, and insulin sensitivity indices after 8 weeks of taurine or placebo supplementation

	Placebo				Taurine			
	Basal		8 weeks		Basal		8 weeks	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
Metabolic profile								
Glycemia (mg/dL)	89[a]	3	92[a]	3	89[a]	3	85[a]	2
Insulin (mU/L)	25[a]	4	25[a]	5	17[ab]	2	15[b]	2
HOMA-IR	5.6[a]	1.0	5.8[a]	1.2	3.8[ab]	0.5	2.9[b]	0.4
HMW adiponectin (µg/mL)	2.0[a]	0.4	1.9[a]	0.4	4.1[b]	1.0	4.7[c]	1.0
Sulfur amino acids								
Cysteine (µmol/L)	263[a]	19	285[a]	10	291[a]	13	283[a]	13
Methionine (µmol/L)	27[a]	4	24[a]	1	26[a]	1	23[a]	2
Homocysteine (µmol/L)	6.7[a]	1.5	6.1[a]	1.2	5.6[a]	0.4	5.3[a]	0.6
Oxidative stress markers								
TBARS (µmol/L)	24[a]	3	20[a]	1	20[a]	1	16[b]	1
AOPP (µmol/L)	198[a]	36	183[a]	27	147[a]	21	145[a]	12
FRAP (µmol/L)	1,014[a]	105	1,094[a]	90	957[a]	117	997[a]	90
GSH (µmol/L)	435[a]	31	517[a]	23	448[a]	57	433[a]	22
α-Tocopherol (µmol/L)	16[a]	1	15[ab]	1	13[b]	1	13[b]	1

SEM standard error of the mean, *HOMA-IR* homeostatic model assessment of insulin resistance, *HMW adiponectin* high molecular weight adiponectin, *TBARS* thiobarbituric acid reactive species, *AOPP* advanced oxidation protein products, *FRAP* ferric-reducing antioxidant power, *GSH* reduced glutathione. Different letters means significant difference within or between groups ($p < 0.05$; linear mixed model)

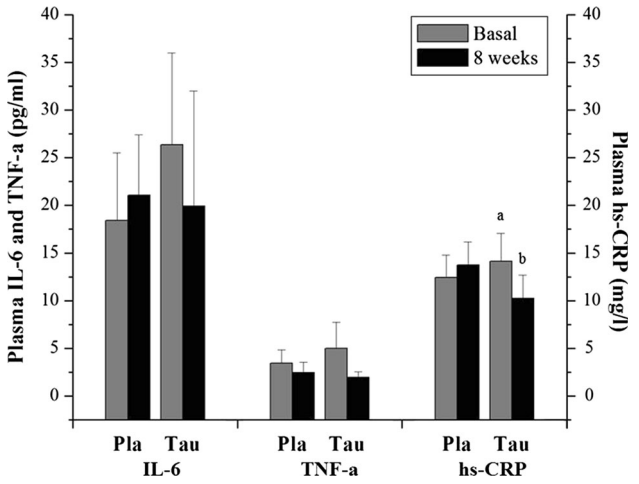

Fig. 2 Obese women plasma concentrations of interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and high-sensitive C-reactive protein (hs-CRP) after 8 weeks of taurine (Tau) or placebo (Pla) supplementation. Data are reported as mean and standard error. *Different letters* means significant difference ($p < 0.05$; linear mixed model)

group [28]. Oliveira et al. [14] found that Tau at physiological concentrations was able to sequester reactive oxygen species (peroxyl and superoxide radicals) and reactive nitrogen species (peroxynitrite). The authors also demonstrated that Tau has the potential to protect against lipid peroxidation and to maintain total thiol concentration in hepatic tissue of Wistar rats. Supplementation of S-containing amino acids may play an effective role in the maintenance of GSH levels [29], and Tau may also contribute to this preservation by increasing the availability of cysteine to GSH synthesis.

The anti-inflammatory action seems to be related to the antioxidant ability of Tau to neutralize hypochlorous acid by forming taurine chloramine, a relatively more stable and less toxic compound. The taurine chloramine can be produced at the site of inflammation and regulate expression and secretion of cytokines such as nitric oxide, IL-6, IL-8, and TNF-α [9]. The mechanism involves the inhibition of nuclear factor *kappa* B activation by oxidation of the inhibitory protein IκB-α [10]. The present results show that 8-week Tau supplementation reduced plasma hs-CRP concentrations, but not TNF-α and IL-6. Studies evaluating the effects of Tau supplementation in obesity are rare, and the protective anti-inflammatory activity of Tau in humans is still poorly known. However, two studies demonstrated significant reduction in hs-CRP [30] and improvement of insulin sensitivity [31] in insulin resistant men and women (IMC >25 kg/m^2) receiving a diet containing cod as the main protein source for 2 weeks. This diet was compared to an isocaloric one, in which protein source was from lean meat of animals other than fish, eggs, skim milk, and derivatives. The authors suggest that the results are related to the amino acids composition of cod fish, especially taurine [30, 31].

Besides the reduction in hs-CRP levels, taurine supplementation also improved adiponectin values in the studied volunteers. Engeli et al. [32] demonstrated an inverse association between adiponectin concentrations and inflammatory markers such as CRP in obese women. Moreover, treatment of 3T3-L1 adipocytes with 25 μg/mL of CRP in vitro promoted an inhibition of 31 % in adiponectin mRNA expression [33]. These data point out a possible relation between the reduction in hs-CRP and the rise in adiponectin levels by Tau supplementation evidenced in the present study. Experimental studies on nonalcoholic steatohepatitis [34] and ethanol-induced hepatic steatosis [35] rats also demonstrated effects of Tau on adiponectin. The authors showed that Tau increased the expression of adiponectin mRNA in liver [34] and subcutaneous adipose tissue [35] and prevented decreases in serum adiponectin.

The presence of adiponectin receptors at liver and skeletal muscles was described [36], and increased levels of adiponectin in blood, especially high molecular weight adiponectin, were associated with improvement of insulin sensitivity [37]. In the present study, insulin resistance was evidenced in the obese women by increased insulin and HOMA-IR values (Table 1). Although reductions in glycemia, insulin, and HOMA-IR were observed only in Tau-supplemented group, these reductions did not show statistical significance. Few studies concerning the effect of Tau on glucose homeostasis in humans were found. Besides the antioxidant effect previously described, Xiao et al. [13] also observed that Tau supplementation prevented the reduction in insulin sensitivity induced by intravenous lipid infusion in humans. In contrast, another study conducted on men with genetic predisposition to type 2 diabetes did not demonstrate any effect of Tau on insulin secretion and/or sensitivity after 8 weeks of supplementation with 1.5 g per day [38]. In animal studies, Tau supplementation has positive results on glucose metabolism. Haber et al. [15] demonstrated that Tau infusion together with a high glucose concentration prevented the hyperglycemia-induced insulin resistance in rats. Oprescu et al. [16] observed that islets and MIN6 cells exposed to free fatty acids showed decreased glucose-stimulated insulin secretion that was prevented by Tau confusion.

The present study has limitations that should be taken into consideration before drawing conclusions. The placebo- and taurine-supplemented groups presented significant different concentrations of insulin, HOMA-IR, adiponectin, and TBARS at baseline. It happened due to the impossibility to control biomarkers before the beginning of experiment and the great variance of some biomarkers in humans. However, it is important to note that

this was a paired study in which each subject was considered his own control, and all statistical analyses took into account the basal data for each volunteer minimizing its influence on final results. Moreover, the small sample size impairs definitive conclusions, especially regarding the inflammation markers IL-6 and TNF-α, which presented a wide range of variation. However, the majority of studies evaluating the beneficial effects of Tau come from in vitro and animal models research. To the best of our knowledge, this is one of the first studies to evaluate the effects of taurine supplementation in obese humans.

Based on the present results, it is possible to conclude that 8 weeks of taurine supplementation associated with nutritional counseling is able to ease obesity complications increasing adiponectin levels and decreasing lipid peroxidation marker TBARS and inflammatory marker hs-CRP. These results were previously demonstrated only in animal and in vitro studies. These data point out taurine as a conditionally essential amino acid in obesity which, after more studies, may be helpful in obesity treatment.

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Conflict of interest The authors declare that they have no conflict of interest.

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