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Effect of taurine on glycaemic, lipid and inflammatory profile in individuals with type 2 diabetes: study protocol of a randomised trial

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Abstract

Type 2 diabetes mellitus (T2DM) is characterised by chronic hyperglycaemia. Despite the efficacy of conventional pharmacotherapy, some individuals do not reach glycaemic goals and require adjuvant therapies. Taurine, a semi-essential amino acid, decreases blood glucose and cholesterol levels in rodents and humans. However, glycated hemoglobin (HbA1c) has not been evaluated in randomised controlled trials after taurine treatment for more than 12 weeks. This study aims to evaluate the effect of taurine administration on glycaemic, lipid, inflammatory, anthropometric and dietary parameters in individuals with T2DM. A randomised, double-blind, placebo-controlled clinical trial will be conducted at the Clinical Research Center of a tertiary public hospital. Participants with T2DM (*n* 94) will be recruited and randomised to receive 3 g of taurine or placebo, twice/day, orally, for 12 weeks. Blood samples will be collected before and after 12 weeks of treatment, when HbA1c, fasting glucose, insulin, albuminuria, creatinine, total cholesterol and fractions, triglycerides, C-reactive protein, TNF-α, IL 1, 4, 5, 6, 10 and 13 will be evaluated. Anthropometric parameters and 24-hour food recall will also be evaluated. The study will evaluate the effect of taurine treatment on biochemical and anthropometric parameters in individuals with T2DM. These results will guide the decision-making to indicate taurine treatment as an adjunct in individuals with T2DM who have not reached their glycaemic goal.

Key words: **Taurine: Diabetes mellitus: Cholesterol: Cytokines: Glycated hemoglobin: Hyperglycaemia**

Diabetes caused 1·5 million deaths in 2019[1]. Adults with diabetes mellitus should have 7·0 % target glycated hemoglobin (HbA1c) to reduce chronic microvascular complications and the occurrence of acute myocardial infarction[2]. Diabetes pharmacotherapy, associated with nutritional and physical activity, is indicated to achieve the HbA1c target. The combination of different drug classes such as biguanides, sulfonylureas, glucagon-like peptide 1 (GLP-1) agonists, sodium-glucose transport protein 2 (SGLT2) inhibitors and others are essential for type 2 diabetes mellitus (T2DM) treatment[3,4]. However, some individuals do not reach the glycaemic targets with these conventional therapies. Because adequate glycaemic control is associated with a lower incidence of chronic complications of diabetes[5], other adjuvants to conventional therapy could be effective and safe agents in the treatment of the disease.

Taurine is a semi-essential amino acid that humans cannot synthesise in large amounts. Food intake or supplementation are essential sources of taurine[6]. It plays a role in many physiological processes, including hypoglycaemic properties[7]. Preclinical studies show that taurine has an antidepressant[8], neuromodulator, neuroprotective and nephroprotective effect in animals with diabetes[9–11]. Moreover, taurine reduces blood glucose by 18 % after the second week of its administration in rats with streptozotocin-induced diabetes[8]. Taurine also reduces palatable food intake in rats with and without diabetes, suggesting effects on satiety mechanisms[12]. Furthermore, taurine improves glucose tolerance, reduces the expression of gluconeogenic genes, increases the hepatic expression of genes involved in glycolysis and can improve hepatic insulin signalling[13]. Therefore, these mechanisms may reduce blood

Abbreviations: HbA1c, glycated HbA1C; T2DM, type 2 diabetes mellitus.

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glucose levels in animals with diabetes. Since individuals with diabetes have low levels of plasma taurine[14,15], its use can be helpful as adjuvant therapy.

In a recent meta-analysis authors concluded that taurine supplementation was associated with HbA1c, fasting glycaemia and insulin resistance reduction, but was not associated with changes in insulin or lipid profile in individuals with diabetes[16]. However, this meta-analysis included only five studies, mergin results from type 1 diabetes mellitus (T1DM)[17] and T2DM, combined taurine and N-acetylcysteine administration without the taurine group as a comparator[18] or positive effect only if combined with resistance exercise[19]. Moreover, this meta-analysis included studies with treatment regimens shorter than 12 weeks[20,21] and patients with different comorbidities[20,21]. Another clinical trial, not included in that meta-analysis showed that taurine supplementation (3 g/d) for 4 months did not change HbA1c levels or fasting glycaemia in 22 participants with T2DM[22]. Similar results were found by Maleki et al.[7], who showed a reduction in fasting glycaemia, insulinaemia, insulin resistance, total cholesterol and LDL-cholesterol, with an increase in HDL-cholesterol levels, but without HbA1c changes after two months in 23 participants with T2DM. In these studies, a small sample size, low doses of taurine or short follow-up may have compromised favourable results of taurine administration on HbA1c levels.

Due to few well-conducted clinical trials, we will perform a randomised, double-blind, placebo-controlled, parallel study, exploring the anti-diabetic properties of taurine in T2DM. We hypothesise that chronic taurine administration (6 g/d for 12 weeks) will reduce HbA1c levels and improve the lipid and inflammatory profile.

Materials and methods

Study design and setting

This randomised, double-blind, parallel, placebo-controlled clinical trial will be conducted at a tertiary public hospital in Southern Brazil. This study protocol adheres to the SPIRIT statement[23].

This study is conducted in accordance with the Declaration of Helsinki and was approved by the Scientific Committee and Research Ethical Commission of Hospital de Clínicas de Porto Alegre (Brazil) (Certificate of Presentation for Ethical Appreciation 38900420·3·0000·5327).

Eligibility criteria

Table 1 shows the eligibility criteria.

Interventions

Volunteers who meet the inclusion criteria will be asked to sign a written informed consent before enrolment in the trial. Participants will be randomised into intervention or control groups. In the intervention group, participants will receive 3 g of taurine, twice a day, as a powder for oral suspension (3 g/sachet), for 12 weeks. Participants will be recommended to take the taurine immediately before breakfast and dinner.

Table 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
1. Female and male individuals, with clinical diagnosis of T2DM for at least 6 months	1. Use of herbal supplements, antioxidants and multivitamins in the last 3 months
2. Age over 30 and lower than 80 years	2. Pregnancy or lactation
3. BMI equal to or above 18·5 kg/m^2, without weight change in the last 3 months	3. Myocardial infarction in the last 6 months
4. HbA1c between 7·5 % and 10·5 %	4. Current neoplasia
5. Stable anti-diabetic therapy for at least 3 months	5. Chronic use of glucocorticoids
	6. Bariatric surgery
	7. Insulin use

Abbreviations: T2DM, type 2 diabetes mellitus; BMI, body mass index; HbA1c, glycated hemoglobin.

This taurine dose was chosen based on an equivalent dose from a preclinical study with a glycaemic reduction in animals with diabetes[8], as well as from clinical intervention studies for safety[24,25].

Participants in the placebo group will receive 3 g vehicle (micronised cellulose), twice/day by oral administration for 12 weeks, with identical sachets as those from taurine.

Strategies for trial retention

Participants will receive phone calls once a week to monitor their daily adherence and adverse events. Moreover, participants will be asked to monthly return their empty boxes on the face-to-face visits. Phone calls or messages will also be used to remember participants regarding scheduled or missed visits.

Study outcomes

The primary outcome will be HbA1c levels after 12 weeks of treatment.

A set of secondary clinical outcomes will include fasting glucose and insulin plasma levels, insulin resistance (evaluated by Homeostatic Model Assessment index, HOMA-IR), albuminuria, creatinine and glucose variability evaluated with continuous glucose monitoring along 2 weeks, total-, LDL- and HDL-cholesterol levels, triglycerides, C-reactive protein levels, TNF-α, IL-1, IL-4, IL-5, IL-6, IL-10 and IL-13 inflammatory cytokines levels. These outcomes will be evaluated at baseline and at the end of the study (12th week).

Recruitment and participant timeline

The recruitment period for the study will be from April 2021 to August 2023. Participants will be invited to participate in the study by announcement in newspaper, electronic and social media. Participants will visit the hospital six times. Figure 1 shows the flow diagram of the study design.

Statistical considerations

For assessment of the taurine effect on HbA1c levels, we assumed an 80 % power, a 5 % significance level and a minimum

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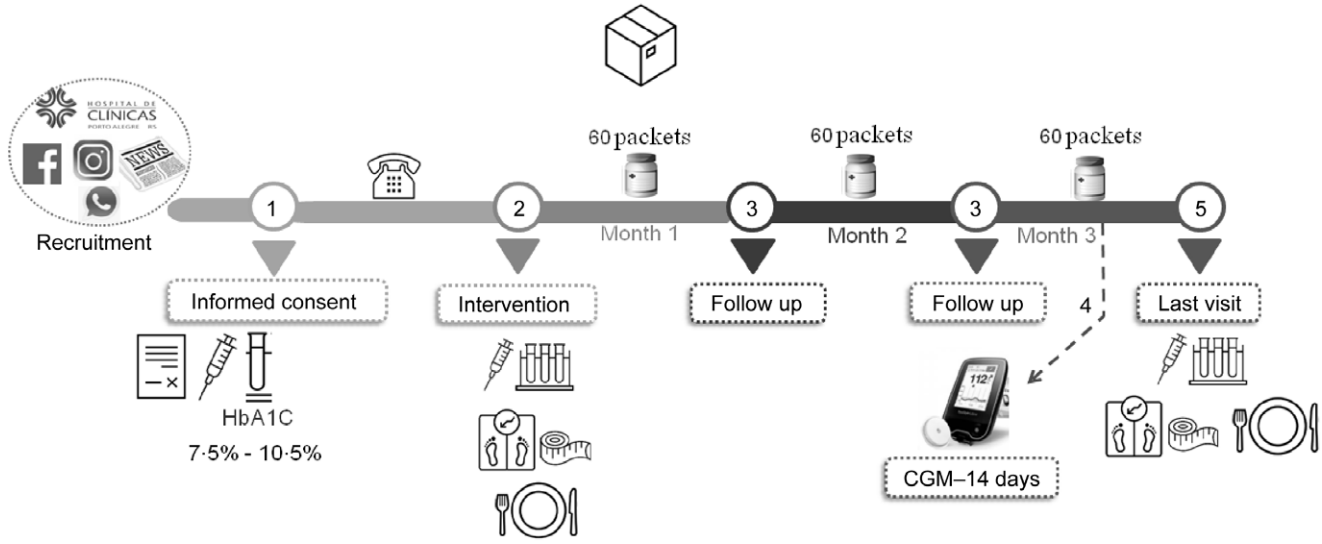

Fig. 1. Flow diagram of the study design. (1) presentation of the study, signing of the informed consent form and collection of glycated hemoglobin (HbA1c). (2) baseline data collection, dietary recall, anthropometric measurements, delivery of the box with taurine/placebo and begining of the intervention. (3) monthly delivery of the box with taurine/placebo and weight measurement. (4) insertion of the continuous glucose monitoring system (CGM). (5) end of the study, CGM removal, data collection, dietary recall, anthropometric measurements and collection of additional tests.

difference of 0·5 % in the HbA1c levels between groups post-intervention. We estimated a 20 % dropout rate and considered the variations from the study by Pinto et al.[26]. The total number calculated was 94; half of them will receive taurine and half will receive placebo (Winpepi software)[27]. The randomly assigned participant's data will be analysed according to the intention-to-treat principle and to the per-protocol principle, with treatment, time and treatment–time interaction registered as the fixed effects. We will qualitatively document reasons and details of each case of withdrawal. The primary hypothesis will be tested on a superiority framework. The Statistical Package for Social Science Professional software version 20·0 (IBM Corp.) will be used for these analyses. The normality of the data will be tested by the Shapiro–Wilk test. Mean and standard deviations will be used to describe the parametric continuous variables and the median and interquartile ranges for non-parametric variables, while absolute and relative frequencies will be used for categorical variables. The socio-demographic and biochemistry/immunologic results will be correlated by Pearson's test. Student's *t* test or Mann–Whitney test will be used to compare outcomes. Treatment effects (group, time and group interaction) will be estimated using Generalised Estimation Equations followed by the Bonferroni posthoc test ($P < 0{\cdot}05$). A multiple linear regression analysis (backward method) will be performed to investigate the impact of routine pharmacotherapy on the primary and secondary outcomes.

Allocation

Numeric codes for each treatment will be provided by a pharmacist responsible for taurine or placebo sachets preparation (Farmácia Marcela®). This pharmacist is not connected to the study and detains the treatment code. Participants will be randomly assigned to the intervention or placebo group according to a sequence of computer-generated random numbers. This sequence will be obtained in the Excel Microsoft program, in a 1:1 ratio, with blocks of eight and the last block with six participants to complete the total number calculated. A sealed envelope containing the allocation code will be opened only at the beginning of treatment in the participant's presence, according to the order of entry into the study.

All trial participants, health care providers, outcome raters and data analysts will be blinded to the treatment interventions. Participants will receive a box with 60 sachets with numeric codes and administration instructions. The sachets of taurine or placebo will be of the same size, weight and appearance. Blood samples will be identified by the entrance in the study from 1 to 94, without other additional information. Unblinding will be allowed only after a severe adverse event and directly sent to the participant's personal physician. In case of unintentional violation of confidentiality for any reason, the researcher involved will notify the main researcher and the treatment codes will be changed.

Data collection and management

A questionnaire will be applied to obtain the socio-demographic and clinical characteristics of participants, including age, sex, marital status, schooling level, diabetes duration, family history of diabetes and self-reported physical activity. Drugs for T2DM or comorbidities and nutritional supplements will be registered at baseline and at the end of the study.

Blood samples will be collected and centrifuged at 1000 g for 10 min to separate plasma or serum, which will be stored for further analysis of biochemical parameters. Urinary samples will be obtained for albumin measurement (immunoturbidimetry, Abbott; Alinity C). The HbA1c will be analysed by HPLC (Variant II Turbo the Biorat). Plasma glucose will be determined

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by the enzymatic method (UV Abbott; Alinity C) and HDL-cholesterol and triglycerides by the enzymatic-colorimetric method (Abbott; Alinity C). C-reactive protein will be determined by the level of immunoturbidimetry (Abbott; Alinity C) and insulin levels by chemiluminescent immunoassay (Abbott; Alinity C). LDL-cholesterol will be calculated by the Friedewald equation. Insulin resistance will be calculated by the Homeostatic Model Assessment (HOMA-IR), based on insulin and fasting glucose levels[28].

For inflammatory biomarkers, the blood will be centrifuged at 1000 g for 10 min and serum will be frozen (–80°C) for further analysis by the enzyme-linked immunosorbent assay (ELISA) technique, using commercial kits: TNF-α, IL-1, IL-4, IL-5, IL-6, IL-10 and IL-13 (Human ELISA Kits, Sigma-Aldrich).

The continuous glucose monitoring sensor device (FreeStyle Libre®, Abbott Laboratories) will be implanted 14 d before the end of the study in the participant's left arm and a scan at 8-hour intervals will record interstitial glucose every 15 min. The device will be removed in the last visit and the stored information will be transferred to a database to analyse the hypo- or hyperglycaemic daily frequency and to calculate glucose variability by the mean glucose excursion amplitude, glucose coefficient of variation (CV%) and glucose standard deviation (SD). These indices, except mean glucose excursion amplitude, will be calculated in a 6-hour timeframe of glucose values to obtain the measures according to the specific period of the day. The mean glucose excursion amplitude index will be calculated for the whole signal and its calculation will be based on the differences between peaks and nadir points, considering those points higher than 1SD[29].

Anthropometry measures, including body weight, height, body mass index BMI (kg/m^2), waist and hip circumferences changes, as well as an evaluation of 24-hour food recall, will be recorded at the first and last visit. The weight will be measured in a digitally calibrated balance with a maximum capacity of 150 kg and a precision of 100 g. The height will be determined by a vertical statometer attached to the balance with a capacity of 2 m/0·1 cm (Welmy®). Waist and hip circumferences will be measured with an inelastic metric tape (2 m/0·1 cm). The food consumption will be registered by the 24-hour recall method (24HR) for all individuals in the baseline and at the end of the study. The values of the food consumption obtained will be used to calculate total calories, proteins, carbohydrates, fats and fiber intake using a commercial software (Diet One®).

Ethical considerations

The study strictly follows the protocols regarding informed consent form, confidentiality and anonymity. An informed consent form with guidelines, objectives of the project, description of procedures, possible risks and benefits will be provided. Participants will also be informed that participation is voluntary, and they can withdraw from the study at any time. The study was approved by the facility's institutional review board in November 2020 (38900420·3·0000·5327) and registered in the Clinical Trials Database (NCT04874012). All files containing the participants' data will be stored in a secure database password-protected document that will be accessed only by authorised members of the research team. The data will be treated in accordance with the Brazilian legislation[30].

Discussion

Adjuvants in conventional therapy could improve T2DM control and prevent chronic complications due to uncontrolled glycaemia. Few studies analysed taurine administration and its effects on HbA1c in humans. Those available trials had some methodological flaws that preclude the use of this amino acid in clinical practice, such as small sample size, low taurine doses and short-term treatment[7,22].

Due to taurine low levels in individuals with diabetes, combined with its scarce source by food intake, we believe that taurine may be important to lower glycemic and possibly prevent chronic complications associated with T2DM[31–33]. This randomised, double-blind, placebo-controlled, parallel, exploratory clinical trial will determine the efficacy of 6 g/d taurine in decreasing 0·5 % HbA1c when added to conventional therapy in individuals with T2DM. Because every 1 % increase in HbA1c is associated with a 25 % increase in the hazard of cardiovascular mortality and a 15 % risk of all-cause mortality in T2DM[34], the multiple taurine effects might contribute to lower mortality risk in these individuals.

Our study is the first to evaluate the efficacy of a high dose of taurine (6 g/d), for 12 weeks, in glucose, lipid and inflammatory profile and renal markers in individuals with T2DM. This dose derives from the dose used in preclinical studies (100 mg/kg) performed at our laboratory, in which we observed positive results in the blood glucose of rats with streptozotocin-induced diabetes as well from clinical studies[6,8,9,12,24]. Moreover, we will maintain the experimental protocol for 12 weeks, which is the time necessary to obtain changes in the main parameter of diabetes control, HbA1c.

Previous studies showed that taurine supplementation, 6 g/d for 3 weeks, mitigated an increase in total and LDL-cholesterol in healthy young men fed with an experimental high-fat-cholesterol diet, despite its increased VLDL-cholesterol and triglycerides[24]. Seven weeks of supplementation with taurine (3 g/d) decreases serum triglyceride levels and improves the atherogenic index in overweight/obese individuals[33]. Moreover, the individuals under taurine supplementation decreased their body weight by 2 %[33]. The taurine effect on lipid profile may prevent diabetic-related complications since dyslipidaemia is a risk factor for cardiovascular disease in individuals with T2DM[35]. Pre-clinical studies show tha taurine also has an antioxidant and anti-inflammatory effect in animals, reducing pro-oxidative and inflammatory biomarkers in different tissues as brain, heart, skeletal muscle and kidney[9,11,36,37,38]. However, anti-inflammatory and nephroprotective properties were not evaluated in studies in humans with diabetes.

We hope to identify a reduction on HbA1c and an improvement in the lipid and inflammatory profile, as well as in the anthropometric parameters with taurine use in people with T2DM. Due to its multiplicity of antioxidant and anti-

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inflammatory effects, taurine may prevent comorbidities commonly associated with chronic hyperglycaemia. The use of this amino acid as an adjuvant of treatment may improve the quality of life of individuals with T2DM, delaying the onset of chronic complications and reducing health costs. Such information will have immediate applicability in the promotion of public health.

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The authors declare no conflicts of interest.

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