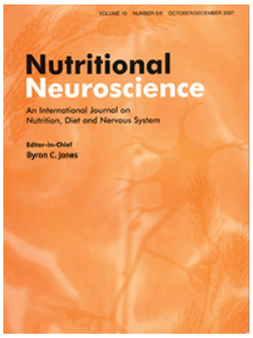

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Nutritional Neuroscience

An International Journal on Nutrition, Diet and Nervous System

ISSN: 1028-415X (Print) 1476-8305 (Online) Journal homepage: https://www.tandfonline.com/loi/ynns20

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To cite this article: Gabriella Richter Natividade, Carina de Araujo, Raquel Crespo Fitz, Elisa Brietzke, Pedro Schestatsky & Fernando Gerchman (2019): Psychiatric profile and quality of life of subjects with excess weight treated with transcranial direct current stimulation combined with a hypocaloric diet, Nutritional Neuroscience, DOI: 10.1080/1028415X.2019.1693319

To link to this article: https://doi.org/10.1080/1028415X.2019.1693319

Published online: 22 Nov 2019.

NUTRITIONAL NEUROSCIENCE
https://doi.org/10.1080/1028415X.2019.1693319

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Psychiatric profile and quality of life of subjects with excess weight treated with transcranial direct current stimulation combined with a hypocaloric diet*

Gabriella Richter Natividade [a,b], Carina de Araujo [a,b], Raquel Crespo Fitz [a,b], Elisa Brietzke [c], Pedro Schestatsky [a] and Fernando Gerchman [a,b,d]

[a]Faculdade de Medicina, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil; [b]Postgraduate Program in Medical Science: Endocrinology, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil; [c]Department of Psychiatry, Queens University School of Medicine, Kingston, ON, Canada; [d]Division of Endocrinology and Metabolism, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil

ABSTRACT

Background: Transcranial direct current stimulation (tDCS) of the dorsolateral prefrontal cortex (DLPFC) may reduce appetite and caloric intake and may be able to play a role as an adjunct treatment for obesity. Stimulation of this brain area is also used for the treatment of depression, which shares a common pathophysiology with obesity. As a result, the effect of tDCS on mental health and its impact on the quality of life of subjects with excess weight needs to be addressed.
Objective: To assess the effect of daily tDCS of the right DLPFC on mood, daytime sleepiness, anxiety and quality of life in subjects with excess weight on a hypocaloric diet.
Methods: We randomly assigned 28 subjects to receive 20 sessions of active or sham tDCS over the right DLPFC for 20 consecutive weekdays. The severity of depressive and anxiety symptoms was assessed by the Beck Depression Inventory (BDI) and the State-Trait Anxiety Inventory-State (STAI-S). Sleepiness was measured by a daytime sleepiness questionnaire (DSQ), and quality of life was measured by the 36-Item Short Form Health Survey (SF-36).
Results: There were no significant changes in BDI, STAI-S and DSQ scores between groups, even after adjustments for the use of antidepressant medications and changes in body weight. There were also no significant changes in different subscales of the SF-36 quality of life questionnaire between groups.
Conclusion: Repetitive tDCS on the right DLPFC is not associated with impairment in mental health or quality of life in overweight and obese subjects.

KEYWORDS
TDCS; depressive symptoms; anxiety; quality of life; excess weight; sleepiness; DLPFC; adverse effects

Introduction

Food intake is affected by appetite regulation in the hypothalamus and other brain areas, such as the dorsolateral prefrontal cortex (DLPFC), that participate in the integration of incoming sensory signals and emotional information [1]. The DLPFC is primarily responsible for higher cognitive functioning, such as reward evaluation and cognitive control over overeating and emotions [2,3]. A lack of integration between the cognitive control areas of the DLPFC and reward areas may explain impulsive behaviour, often tied to overeating and obesity [4]. This connection was demonstrated in a study in which subjects with obesity showed a reduction in striatal dopamine D2 receptor availability compared with lean subjects, as assessed through positron emission tomography (PET). These results were further associated with a reduction in brain glucose metabolism in the DLPFC of those with obesity, suggesting that the hypoactivity of the DLPFC may be related to an inability to control overeating [5–8]. Therefore, interventions that could restore the activity of the DLPFC, such as brain stimulation, may have a potential role in reducing the desire to eat and reducing calorie intake [9].

Major depression is also associated with an imbalance of left and right prefrontal cortex activation [10]. While depressive individuals have reduced resting-state electroencephalography (EEG) activity over the left prefrontal cortex, they have increased EEG activity over the right prefrontal cortex [11]. Indeed, treatment of depression leading to symptom relief is associated with partial or total restauration of EEG activity in the DLPFC in both hemispheres. As a result, neuromodulation of these areas may have a potential role in the regulation of food intake and behavioural aspects related to excess weight, such as mood, sleep and quality of life [12].

Transcranial direct current stimulation (tDCS) is a non-invasive neuromodulation technique that modifies

CONTACT Carina de Araujo carinanutri@hotmail.com Division of Endocrinology and Metabolism, Hospital de Clínicas de Porto Alegre, Rua Ramiro Barcelos 2350, Anexo, 4° andar. CEP: 90035-003, Porto Alegre, Rio Grande do Sul, Brazil
*GRN and CA shared the first author status.

cortical activity through two electrodes placed over the scalp [13]. The effects of tDCS depend on the direction of the electric current: while cathodal stimulation causes hyperpolarization, leading to decreases in cerebral excitability, anodal stimulation enhances cerebral excitability by increasing the resting membrane potential [14]. The primary mechanism of this technique is a subthreshold alteration in the resting membrane potential, whereas the after-effects depend on protein expression, changes in intracellular cyclic AMP concentration, and the synaptic plasticity of glutamatergic connections [13].

In short-term studies, the application of brain tDCS resulted in a reduction in caloric intake after anodal stimulation of the right [15] and left DLPFC [16]. In a crossover clinical trial with nine subjects who were submitted to anodal tDCS targeting the left DLPFC, there was a significant decrease in calorie intake from soda and fat following three consecutive tDCS sessions compared to cathodal stimulation [17]. Regarding mood, several studies reported that anodal tDCS over the left DLPFC and cathodal stimulation over different intra- or extra-cephalic regions (for example, the right supraorbital area, right upper arm and right DLPFC) improved symptoms of major depression [18]. In a randomised, double-blinded study, anodal tDCS over the left DLPFC and cathodal tDCS over the right DLPFC improved depressive symptoms in comparison to sham tDCS [19].

Obesity is frequently associated with depression, sleep disturbances, anxiety, and impaired quality of life [20,21]. Since obesity and depressive disorders may share a pathophysiology and are common comorbidities, we aim to analyse the psychosocial health status and quality of life of overweight and obese subjects treated with tDCS in association with a hypocaloric diet.

Materials and methods

This was a secondary analysis from a randomised, double-blind, placebo-controlled clinical trial (ClinicalTrials.gov NCT02683902). Full details of the protocol have been published elsewhere [22]. The study was conducted at Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Brazil, and it was approved by the local ethics committee (CAAE 42996915.0.0000.5327).

Twenty-eight participants were randomly assigned to two groups in a 1:1 ratio, stratified by sex: active tDCS plus hypocaloric diet or sham tDCS plus hypocaloric diet. The participants and the investigators, except those who applied tDCS, were blinded to the groups' interventions. The study included participants of either sex, who were 20–50 years old, with a body mass index between 25 and 35 kg/m^2 at screening and who had maintained a stable weight for at least 12 weeks. It was recommended the participants improve their dietary habits, and they were submitted to a low calorie diet aiming to reduce their initial body weight by 3% over the four-week treatment. A history of active substance abuse within the past year, severe depression or other severe psychiatric comorbidities were exclusion criteria. Participants were recruited via advertisements on the Hospital de Clínicas de Porto Alegre website, in a local newspaper, and on television or through referral by physicians or nutritionists from clinics in the metropolitan area of Porto Alegre, Brazil. All participants provided written informed consent prior to their enrolment.

The intervention with tDCS was administered at 2 mA for 20 min per day on 20 consecutive weekdays. The anode electrode was placed over the right DLPFC (F4), and the cathode electrode was placed over the left DLPFC (F3), according to the 10–20 International System of Electrode Placement (10–20 EEG system). For active tDCS, the current was ramped up until it reached 2 mA. After 20 min, the current was ramped down and then turned off. For sham tDCS, the current was ramped up to 2 mA and then back down in the first and last 30 s of the 20-minute session. As a result, the participants in the sham group were able to feel the initial itching sensation associated with turning on the device. The stimulation procedure was repeated for 20 consecutive weekdays. To reduce the probability of dropout and to reduce the effect of expectation for tDCS outcomes in the results, we developed a consent form in which participants were informed that they could receive two different current intensities ('low', i.e. the one given to the sham group, or 'high', i.e. the one given to the active group). As a result, participants were led to believe that there was no placebo condition. To assess the integrity of the blinding procedure, at the end of the study, participants were asked to guess which intervention they had received: low or high intensity.

Questionnaires were administered before and after the intervention period. The Beck Depression Inventory (BDI) was used to evaluate the severity of depressive symptoms (with higher scores indicating higher severity) [23,24]. A daytime sleepiness questionnaire (DSQ) was used to evaluate the occurrence of daytime sleepiness according to five questions derived from the Epworth sleepiness scale [25], in which a higher score indicated a higher level of sleepiness. The severity of anxiety symptoms was assessed using the State-Trait Anxiety Inventory-State (STAI-S), which measures how much anxiety a person feels 'right now, at this moment'; a higher score represents higher anxiety at a particular

moment [26]. The Short Form Health Survey (SF-36) measured quality of life based on 36 questions assessing eight domains of health: physical functioning, physical role, bodily pain, general health, vitality, social functioning, emotional role, and mental health [27]. Higher scores on all SF-36 subscales indicate more favourable levels of functioning. Treatment-emergent adverse events were assessed with the use of a standard questionnaire regarding possible adverse events commonly related to tDCS [28,29], twice each week to assess the acute effects of tDCS after a session and the post-effect between sessions.

All analyses were performed on an intention-to-treat and per-protocol basis. Descriptive statistics were presented as the means and SD and absolute number (%). Student's t-test and the chi-square test were used as appropriate. The differences between scores measured during intervention were analysed using a mixed linear model, adjusted for percentage of weight change and the presence of antidepressant pharmacological treatment. The results of these models were expressed as the mean and SEM, which is considered a more appropriate approach in mixed linear models. The level of statistical significance was set at 0.05. All statistical tests were performed using the software IBM SPSS Statistics, version 19.0 (IBM, Armonk, NY, USA).

Results

Of the 422 subjects screened, 31 were considered eligible in a face-to-face screening, and 28 were randomised and included in an intention-to-treat analysis. The mean age of all participants was 37.6 y (SD = 5.8 y). Twenty-three received all 20 planned sessions and completed the 4-wk assessment (10 participants in the active group and 13 in the sham group), and five received between four and eight tDCS sessions. In the active group, two participants withdrew their consent form, one became a night shift worker, and one was assigned to work in another city. In the sham group, one participant withdrew their consent form. Six participants were using antidepressants (21%), and all of these antidepressants were selective serotonin reuptake inhibitors. In the active group, one participant was taking sertraline. Of the five participants in the sham group under antidepressant treatment, two were taking sertraline, one was taking citalopram, one was taking escitalopram, and one was taking fluoxetine. No participants were taking antipsychotic medication. Of the 21 participants who answered the 'guess your treatment' question, only three correctly guessed when they received real tDCS and three correctly guessed when they received sham tDCS. The subjects' baseline characteristics in the active and sham groups are described in Table 1.

Table 1. Baseline characteristics according to the intervention.[a]

	Active ($n = 14$)	Sham ($n = 14$)	p
Age, y	37.5 ± 7.0	37.7 ± 4.7	0.945
Female sex, *n* (%)	7 (50)	7 (50)	1.000
Ethnicity: white, *n* (%)	10 (71)	11 (79)	0.592
Currently smoking, *n* (%)	2 (14)	1 (7)	0.712
Antidepressant drugs, *n* (%)	1 (7)	5 (35)	0.165
Physical activity, steps/day	5153.0 ± 33167	5783.6 ± 2976.5	0.309[b]
aRMR, kcal/day	1676.9 ± 288.1	1745.1 ± 301.5	0.548[b]
Weight, kg	88.8 ± 12.8	92.0 ± 11.2	0.999
BMI, kg/m^2	31.8 ± 2.6	31.2 ± 2.4	0.482

[a]Data are the absolute number (%) or the mean ± SD. Comparisons between the two groups were tested by Student's *t*-test, and no significant differences were observed between groups.
[b]Statistical analysis was tested on log-transformed data. aRMR, adjusted resting metabolic rate.

The effects of repetitive active tDCS associated with a hypocaloric diet on BDI, STAI-S, DSQ, and SF-36 scores are shown in Figure 1A–D. Differences in BDI and STAI-S scores and the SF-36 subscales were not statistically significant between groups at baseline or over time during the 4-wk intervention. Although the DSQ score showed a trend towards increasing in the active group (Pre-tDCS 5.3, SEM = 1.0; Post-tDCS 6.1, SEM = 0.9) and towards decreasing in the sham group (Pre-tDCS 5.8, SEM = 1.0; Post-tDCS 5.3, SEM = 0.9), the time *vs.* group interaction was not statistically significant ($p = 0.094$) (Figure 1A–D). These results did not change after a per-protocol analysis.

The proportion of participants that reached the aim of a 3% reduction in initial body weight over the 4-wk treatment did not differ between groups (absolute number [%]; active = 7 [50%] and sham = 6 [42.9%]; $p = 1.000$).

Although the frequency of subjects that mentioned feeling tingling, itchiness, scalp burning, pain and sleepiness were higher in the sham group and the frequency of fatigue, hunger, trouble concentrating and nervousness was higher in the active group, these differences were not significantly different, as described in Table 2.

Discussion

Subjects with excess weight have a higher rate of depressive and anxiety symptoms and a lower quality of life than normal-weight controls [30–32]. Hence, it is important to understand the effect of tDCS in association with a hypocaloric diet on psychiatric symptoms and quality of life as an adjunct treatment modality for subjects with excess weight and different diseases.

The use of daily anodal right/cathodal left tDCS over the DLPFC as an intervention in subjects with excess weight did not change mood, daytime sleepiness, anxiety or quality of life, suggesting tDCS is well tolerated. Since

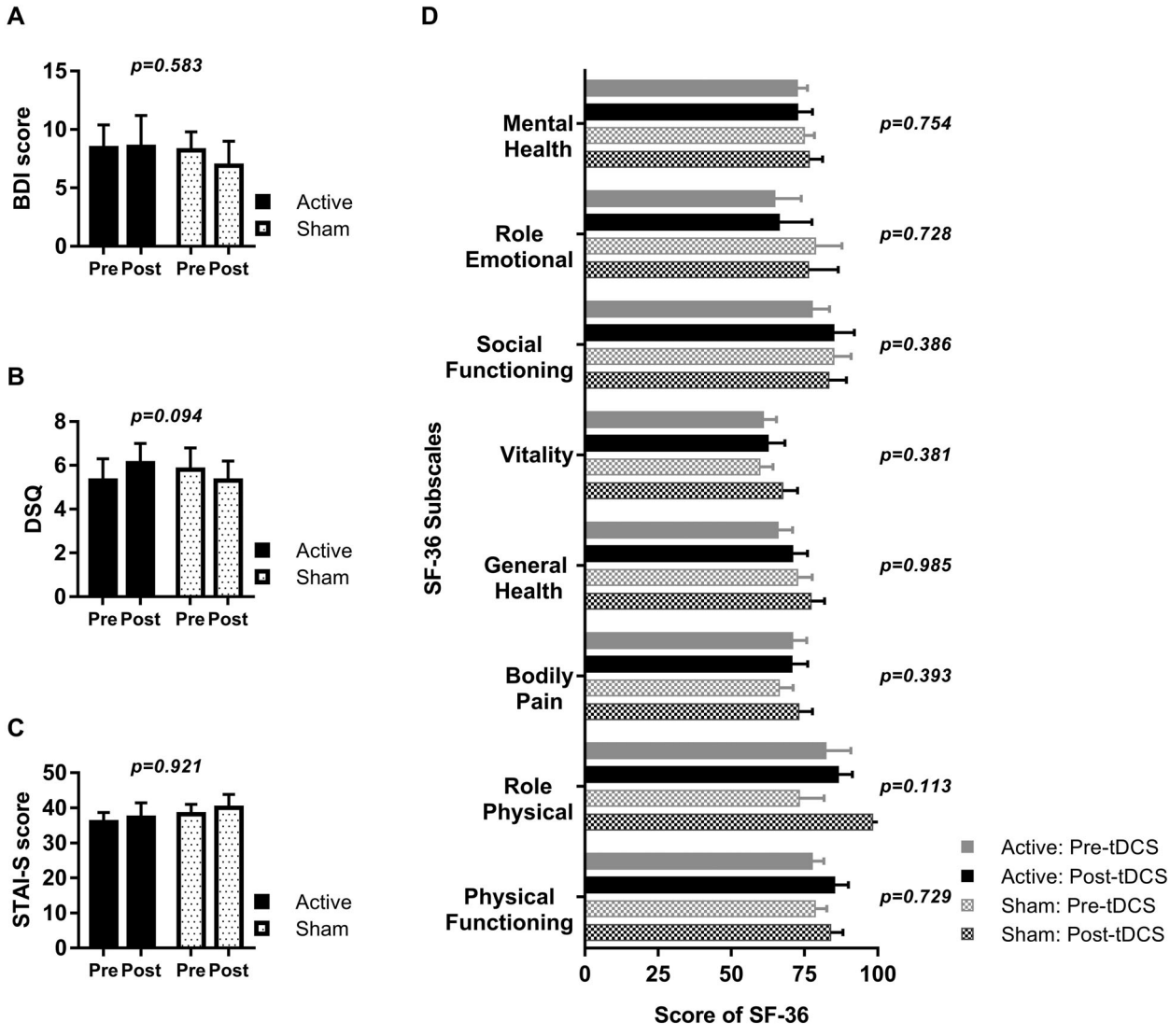

Figure 1. Difference between the final and baseline mean of (A) BDI score, (B) DSQ score, (C) STAI-S score and (D) SF-36 subscales (mean ± SEM). Data were analysed using a mixed linear model, with adjustment for the percentage of weight change and antidepressant pharmacological treatment.

these changes may affect interventions focused on the treatment of obesity [33], our results demonstrated that the active and sham groups were similar and comparable regarding mood, sleep, anxiety, and quality of life. Thus, a mood change did not have the potential to interfere with the effect of the combined treatment of tDCS and a hypocaloric diet in subjects with obesity. As the proportion of participants in each group that achieved a reduction of 3% weight loss was similar, this factor does not seem to be a determinant of our results.

Depression and obesity are often comorbidities and may share aetiological mechanisms [34]. Neuroimaging studies suggest that they exhibit common structural and functional abnormalities in brain regions involved in the regulation of emotion, including the DLPFC [35]. Anodal stimulation over the left DLPFC (F3 in 10–20 EEG system) is considered the standard tDCS protocol for the treatment of subjects with depression [36–38]. However, in our study, a repeated tDCS protocol was applied over the right DLPFC in subjects with excess weight, and the results of different studies suggest that both the right and left DLPFC are involved in eating behaviour and related abnormalities in obese people [16,17,39]. A randomised clinical trial found a reduction in the desire to eat after five days of repetitive tDCS over the right DLPFC in 27 overweight or obese individuals [39]. In contrast, in two other studies, active repetitive stimulation over the left DLPFC in obese subjects found a similar reduction in the desire to eat and in food intake [16,17]. Most of the abovementioned studies used visual analogue scales, and only one assessed depression with a more detailed screening test (Center

Table 2. Assessment of adverse effects frequency according to the treatment group.[a]

	Active ($n = 14$)	Sham ($n = 14$)	P value[b]
During tDCS sessions			
Tingling	6 (42.9)	10 (71.4)	0.252
Itchiness	7 (50.0)	10 (71.4)	0.439
Scalp burning	9 (64.3)	10 (71.4)	1.000
Pain	0.0	2 (14.3)	0.481
Fatigue	4 (28.6)	1 (7.1)	0.326
Disturbed concentration	5 (35.7)	3 (21.4)	0.678
Nervousness	2 (14.3)	1 (7.1)	1.000
Disturbed visual perception	1 (7.1)	0.0	1.000
Sleepiness	3 (21.4)	4 (28.6)	1.000
Other[c]	3 (21.4)	1 (7.1)	0.596
After tDCS sessions			
Tingling	3 (21.4)	3 (21.4)	1.000
Itchiness	5 (35.7)	3 (21.4)	0.678
Scalp burning	5 (35.7)	2 (14.3)	0.385
Pain	2 (14.3)	2 (14.3)	1.000
Fatigue	2 (14.3)	4 (28.6)	0.648
Disturbed concentration	4 (28.6)	1 (7.1)	0.326
Nervousness	3 (21.4)	1 (7.1)	0.596
Nausea	1 (7.1)	1 (7.1)	1.000
Sleeplessness	2 (14.3)	0.0	0.481
Sleepiness	3 (21.4)	3 (21.4)	1.000
Other[d]	1 (7.1)	1 (7.1)	1.000

[a]Data are the absolute numbers (%).
[b]The *P* value for comparisons between the two groups was tested by Fisher's exact test or Yates continuity correction as appropriate.
[c]Sensations classified as 'other': pinching, stinging, and dizziness.
[d]Sensations classified as 'other': local redness, anxiety, sleep improvement, and inappetence.

for Epidemiologic Studies Depression Scale – Revised; CESD-R); similar to us, they used a repetitive anodal tDCS protocol over the right DLPFC, finding no changes between groups over time [39]. Although studies that applied a repetitive anodal tDCS protocol to the left DLPFC in overweight or obese subjects had similar results, it is important to mention that this tDCS protocol is similar to that applied for reducing depressive symptoms. For this reason, perhaps the reduction in desire to eat and food intake found in these studies is partly related to improved mood symptoms. As a result, it is essential to understand in mentally healthy overweight and obese subjects how this interaction occurs and how it affects the effectiveness of intervention with brain tDCS for different purposes in these populations.

A limitation of our study is that severe depression and intense anxiety were exclusion criteria. Several studies showed improvement in depressive symptoms in subjects with major depressive disorder and baseline BDI scores compatible with moderate to severe depression (BDI $\geq$ 26) [19,40,41]. In our study, the presence of average baseline scores within the normal range may be a factor that influenced the absence of changes. In fact, since selective serotonin reuptake inhibitors influence neuroplasticity, they may have a synergistic effect with tDCS on mood through increased cortico-limbic stimulation-induced plasticity [19]. As a consequence, the larger number of participants in the sham group under antidepressant pharmacological treatment needs to be taken into account in ruling out the absence of significant changes in these assessments, even though our results were not affected by adjustments for the use of antidepressant medications.

Although the intervention was applied for four weeks and was not tested for a longer period of time, the tolerability of tDCS in populations with different profiles suggests that this procedure is not harmful in the long term [42]. This study showed that daily anodal right/cathodal left tDCS combined with a hypocaloric diet may be used without causing changes in psychiatric status or quality of life in subjects with excess weight. Future research needs to assess the effect of tDCS on the DLPFC of obese subjects with depression and anxiety, as well as to study the role of tDCS as a neuromodulatory technique for the treatment of obesity.

Acknowledgements

The authors acknowledge Professor Steven E. Kahn from the Department of Metabolism, Endocrinology and Nutrition of the University of Washington and Professor Mirela Jobim de Azevedo (in memoriam) from the Department of Internal Medicine of Universidade Federal do Rio Grande do Sul, who made important contributions to the design of this protocol. Hospital de Clínicas de Porto Alegre Research Fund (FIPE) provided financial support.

Contributors

CA, RCF and FG planned the study; GRN and CA collected the data; GRN, CA and FG analysed the data; GRN, CA, EB, PS and FG interpreted the data; GRN, CA and FG wrote the article; GRN made the figures; all authors read and approved the manuscript before submission. GRN and CA share first author status.

Disclosure statement

No potential conflict of interest was reported by the authors.

Ethics approval

The study was approved by the local ethics committee (CAAE 42996915.0.0000.5327).

Funding

This trial was supported by grants from the Hospital de Clínicas de Porto Alegre Research Fund [FIPE 15-0119], which did not have any role in the study design, data collection or writing of the manuscript.

Notes on contributors

Gabriella Richter Natividade is an undergraduate student in the School of Medicine at Universidade Federal do Rio Grande do Sul, Brazil and is a doctorate student in the Postgraduate Program in Medical Science: Endocrinology in the same school.

Carina de Araujo is a dietician and doctorate student in the Postgraduate Program in Medical Science: Endocrinology from Universidade Federal do Rio Grande do Sul, Porto Alegre, Rio Grande do Sul, Brazil.

Raquel Crespo Fitz is a dietician with a master degree in Medical Science: Endocrinology from Universidade Federal do Rio Grande do Sul, Porto Alegre, Rio Grande do Sul, Brazil.

Elisa Brietzke is a psychiatrist and professor in the Department of Psychiatry, Queen's University School of Medicine, Kingston, Ontario, Canada.

Pedro Schestatsky is professor of the Department of Internal Medicine at the school of Medicine of Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil.

Fernando Gerchman is an Endocrinologist of the Division of Endocrinology and Metabolism of Hospital de Clínicas de Porto Alegre and professor of the Department of Internal Medicine and of the Postgraduate Course in Medical Science: Endocrinology of Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil.

ORCID

Gabriella Richter Natividade http://orcid.org/0000-0002-2811-3619
Carina de Araujo http://orcid.org/0000-0001-5841-0465
Raquel Crespo Fitz http://orcid.org/0000-0002-5689-925X
Elisa Brietzke http://orcid.org/0000-0003-2697-1342
Pedro Schestatsky http://orcid.org/0000-0002-1504-0238
Fernando Gerchman http://orcid.org/0000-0001-5873-9498

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