ORIGINAL ARTICLE

REVISTA ENFERMAGEM ATUAL IN DERME

EFFECTIVENESS OF GINGER IN REDUCING PRESSURE LEVELS IN PERSONS WITH DIABETES: PLACEBO-CONTROLLED RANDOMIZED CLINICAL TRIAL

EFECTIVIDAD DEL JENGIBRE EN LA REDUCCIÓN DE LOS NIVELES DE PRESIÓN EN PERSONAS CON DIABETES: ENSAYO CLÍNICO ALEATORIZADO CONTROLADO CON PLACEBO

EFICÁCIA DO GENGIBRE NA REDUÇÃO DOS NÍVEIS PRESSÓRICOS EM PESSOAS COM DIABETES: ENSAIO CLÍNICO RANDOMIZADO CONTROLADO POR PLACEBO

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ABSTRACT
Objective: to evaluate the effectiveness of ginger in reducing blood pressure in people with type 2 diabetes. Method: randomized, double-blind clinical trial, conducted with people with type 2 diabetes, in primary health care units. Were included individuals aged between 20 and 80 years, using oral antidiabetics and with glycated hemoglobin values between 6% and 10%. The participants were allocated in two distinct groups and randomized in blocks. In the experimental group, participants used 1.2 g of ginger, and in the control group, 1.2 g of a placebo, daily, for 90 days. 103 people completed the study, 47 in the experimental group, and 56 in the control group. Results: the participants in the experimental group showed a reduction in blood pressure values compared to the control group, although not statistically significant. Conclusion: in our analysis, the use of ginger was not able to reduce blood pressure levels in people with diabetes.
Keywords: Blood Pressure; Type 2 Diabetes Mellitus; Ginger; Primary Health Care.

RESUMEN
Objetivo: evaluar la eficacia del jengibre para reducir la presión arterial en personas con diabetes tipo 2. Métodos: ensayo clínico aleatorizado, doble ciego, realizado con personas con diabetes tipo 2, en unidades de atención primaria de salud. Se incluyeron individuos con edades comprendidas entre 20 y 80 años, que usaban antidiabéticos orales y tenían valores de hemoglobina glucosilada entre el 6 y el 10%. Los participantes fueron asignados en dos grupos distintos y asignados al azar en bloques. En el grupo experimental, los participantes utilizaron 1,2 g de jengibre, y en el grupo de control, 1,2 g de un placebo, diariamente, durante 90 días. 103 personas completaron el estudio, 47 en el grupo experimental y 56 en el grupo de control. Resultados: los participantes del grupo experimental mostraron una reducción en los valores de presión arterial en comparación con el grupo control, aunque no estadísticamente significativa. Conclusión: en nuestro análisis, el uso de jengibre no logró reducir los niveles de presión arterial en personas con diabetes.
Palabras clave: Presión Sanguínea. Diabetes Mellitus Tipo 2. Jengibre. Atención Primaria de Salud.

RESUMO
Objetivo: avaliar a eficácia do gengibre na redução da pressão arterial em pessoas com diabetes tipo 2. Método: ensaio clínico randomizado, duplo-cego, realizado com pessoas com diabetes tipo 2, em unidades básicas de saúde. Foram incluídos indivíduos com idade entre 20 e 80 anos, em uso de antidiabéticos orais e com valores de hemoglobina glicada entre 6% e 10%. Os participantes foram alocados em dois grupos distintos e randomizados em blocos. No grupo experimental, os participantes usaram 1,2 g de gengibre e, no grupo controle, 1,2 g de placebo, diariamente, por 90 dias. 103 pessoas completaram o estudo, 47 no grupo experimental e 56 no grupo de controle. Resultados: os participantes do grupo experimental apresentaram redução dos valores pressóricos em relação ao grupo controle, embora sem significância estatística. Conclusão: em nossa análise, o uso de gengibre não foi capaz de reduzir os níveis pressóricos em pessoas com diabetes.
Palavras-chave: Pressão Sanguínea. Diabetes Mellitus Tipo 2. Gengibre. Atenção Primária à Saúde.

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INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) can be characterized as a metabolic and multifactorial dysfunction, which demands continuous care. In the last two decades, the disease has increased from 151 million to 463 million cases worldwide, among people aged 20 to 79 years[1]. In Brazil, almost 20 million people live with the disease, with the country in fifth place in the ranking of those with the highest number of cases, and in third of those who spend the most on the disease[1-2]. Once poorly controlled, diabetes has severe implications for the patient who has the disease, such as micro and macrovascular changes, reduced quality of life, frequent hospitalizations and premature death[1].

Despite efforts to control this disease, factors such as clinical stagnation and low acceptance to the treatment, bring complications that further reinforce the degree of chronicity of the disease, leading to a greater need for care[1-3]. The patient with diabetes also has, in most cases, another correlated disease, arterial hypertension. An explanation for the appearance of these comorbidities is due to the increase in peripheral arterial resistance, caused by vascular remodeling and an increase in the volume of body fluid associated with hyperinsulinemia and hyperglycemia induced by insulin resistance[4]. Deregulation of arterial hypertension among Brazilians is among the main causes of premature deaths registered by the public health system.

Alternatives to mitigate recurrent problems related to diseases like these, have been outlined by the Brazilian government, which in recent years has maximized the use of the so-called Complementary and Integrative Medicine (CAM). Such practices involve natural mechanisms, using safe and effective products and techniques, in addition to contemplating a patient-focused approach. Its insertion in Primary Health Care has gained strength not only due to the countless evidences it presents, but also due to the cost, quality, versatility and variety of resources they have in the management of chronic diseases[5-6].

Among the CAMs available and regulated in the national territory, one stands out for the wide range of products and applications, phytotherapy. Phytotherapy has been used in health promotion and in the treatment of acute and chronic diseases, through the use of medicinal plants in their different pharmaceutical forms[7].

In this scenario, Brazil stands out for having the greatest plant diversity in the world, great empirical application of culturally established medicinal plants and technology to scientifically validate this knowledge. Particularly for the treatment of T2DM, researchers have shown that ginger (*Zingiber officinale*) can be a potential supporting factor in reducing glycemic, lipid

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and even blood pressure levels in this population[8-9].

However, the literature is not unanimous and research on the use of this herbal medicine to reduce blood pressure in people with T2DM is still scarce. Furthermore, to date, no studies of this nature have been identified in the country. Also, the lack of records on the application of herbal medicines like this reflects directly on the clinical practice of nurses, since further clarifications are still needed to legitimize interventions with natural products.

One of the main reasons for the development of this analysis was based on the practical experience of nursing in Basic Health Units linked to Primary Health Care in Brazil. We realized that our patients had high blood pressure values and reported, as well as the need to lower blood glucose, minimize blood pressure values.

The associated problems, forming a cardiometabolic disorder common among patients with Diabetes, cause the risks of complications to accelerate and become more common, spreading a high burden on health systems. Because we have a free public health system, with a population lacking in economic resources, it is imperative to investigate more about the subject. Therefore, the objective of this study was to evaluate the effectiveness of ginger in reducing blood pressure levels in patients with T2DM.

METHODS

Study design

Randomized, double-blind, placebo-controlled and parallel group clinical trial.

Location, participants and eligibility criteria

The study was carried out in seven Basic Health Units (BHU) in the city of Picos, in the region of Vale do Rio Guaribas, in the interior of the state of Piauí, Brazil. The population consisted of people diagnosed with T2DM and associated arterial hypertension, registered and followed up at the BHU where the data were collected. The BHU were chosen at random, through a draw. Units that were operating at least in the morning and afternoon shifts and had people registered and followed up with T2DM diagnoses participated in the draw.

We included people diagnosed with T2DM for at least two years, aged between 20 and 80 years, with preserved cognitive functions - according to the Mini Mental State Examination (MMSE), being treated with oral antidiabetics and glycated hemoglobin (HbA1c) between 6.0% and 10.0% at baseline. The cut-off point established for HbA1c is justified because, with values below 6.0%, people with T2DM already have a good control of this biomarker; and above 10.0%, these already had important deregulations,

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making the application of the research unfeasible[2].

The exclusion criteria used were people using alcohol or tobacco, using any natural product to control diabetes, on insulin therapy, with the presence of chronic changes (cardiovascular, liver, kidney, gastric or mental disorders diagnosed), pregnant women or lactating women. Chronic changes and mental disorder were assessed using information provided by the individuals themselves. People could be discontinued from the study if they experienced any adverse events. The assessment of blood pressure levels was established as a secondary outcome of the research. No cut-off points were established for blood pressure values.

In the city where the research was carried out, there were no records on the number of people with DM2 and HbA1c values between 6.0% and 10.0%, monitored at BHU. Thus, the sample was calculated using the average difference between two groups using the G*Power 3.1.9.2 software, in which a significance level of 5% and a test power of 80% were fixed, based on a previous study[10], totaling 102 people, 51 for each group. However, when considering possible losses, a percentage of 20% was added, totaling 124 people, 62 people for each group.

Data collection

Data collection was carried out from December 2017 to March 2018. In total, 229 people were recruited, and of these, 85 were excluded for the following reasons: 24 did not have HbA1c between 6.0% and 10.0%; 15 used alcohol; 11 did not use oral antidiabetics; 10 used tobacco; nine used insulin; nine had severe cardiovascular problems, and seven had some kidney deficiency.

For recruitment, a previously trained team held meetings with the health professionals of each BHU to explain the objective of the study. Invitation letters and the Free and Informed Consent Term (ICF) were given to community health agents so that they could pass it on to potential research participants, giving them time to read and ask questions about the research. The ICF was only signed after confirming the interest of each of the recruits.

Randomization was created by software and stratified by BHU, with a 1:1 allocation in parallel groups, using random block sizes of six people, based on the HbA1c values. Each person was indicated to participate in a group based on chance, with an equal chance of being allocated to one of the comparison groups.

The allocation sequence was performed by two members of the research group who did not participate directly in the data collection. These were responsible for randomizing the participants into blocks, preparing the bottles, and numbering them. Thus, the principal investigator and the participants were blinded during the

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intervention. For randomization, a numerical list was generated, where the sequence of even numbers corresponded to the Experimental Group (EG), and the sequence of odd numbers to the Control Group (CG). The group in which each person was part was only revealed to the main researcher after analyzing the data.

At the EG, each participant received a bottle containing 60 capsules of ginger (*Zingiber officinale*), per month, for three months. Each capsule contained 600 mg of powdered ginger. In the CG, the participants received a bottle containing 60 placebo capsules (microcrystalline cellulose), per month, for three months. Each capsule contained 600 mg of microcrystalline cellulose. Both the GE and the GC were instructed to take two capsules a day, one 30 minutes before breakfast and the other 30 minutes before lunch.

Both the capsules and the ginger and placebo bottles were the same, to avoid contamination of the investigated, and contained a label with information about the dosage, expiration date of the product and the return date. Each bottle was numbered to facilitate the process of randomization of participants. Within 25 to 29 days a new bottle was delivered. Telephone calls were made to remind participants to look for a new bottle at the BHU in which they were accompanied.

The ginger was processed in powder form and the final product was the 0.1% dry extract. To obtain the raw material, an extraction was performed with water as a solvent and starch as an excipient. The drying was done by spray dryer. The concentration of the extract in water was 33.51% and alcohol 0.89%. The dosage was 0.36% for total gingerols (6-gingerol, 10-gingerol, 6-shogaol). In addition to the physical-chemical test carried out by the manufacturer, the microbiological test and the purity test with heavy metal count were performed. In Brazil, ginger is authorized for use and makes up research exempt from authorization. Both the ginger and the placebo were prepared by a private laboratory, certified by the National Health Surveillance Agency (ANVISA), in accordance with national regulations for drug preparation.

In both groups, participants were encouraged to continue taking routine diabetes medications and to maintain the same eating and exercise habits. In addition, the participants were aware that they could leave the research at any time and for any reason, without prejudice to the health treatment offered by BHU. All this information was extended to the participants' family and/or caregivers.

The collection was divided into two stages. In the first, the participants received instructions about the study and had collected socioeconomic, clinical, and laboratory data.

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It is noteworthy that, for this study, laboratory data were not considered in the analyzes. For data collection, a questionnaire was used containing socioeconomic variables (age, skin color, gender, education level, work activity, income, socioeconomic status, marital status, and who lives with) and clinical variables (mean values of systolic blood pressure and diastolic, time of diagnosis with T2DM, presence of hypertension, frequency of follow-up at the BHU and physical exercise). As they were self-reported, the information provided during data collection at the BHU could have a response bias.

Blood pressure (BP) was measured three times, to establish the mean value, before the beginning of the intervention, and after 90 days, at the end of the intervention. The reference values used are by the VII Brazilian Guideline for Hypertension[11]. To the absent participants, a telephone call or home visit was made to recruit them and schedule new dates for participation. During the follow-up period, participants received a telephone call per month to remind them of the importance of medication adherence, as well as, so that the main researcher could register adverse events. Three months after the delivery of the first bottle containing ginger capsules or placebo, the participants had clinics collected again.

In this research, 142 were randomized, 72 in the EG and 72 in the CG. However, only 103 people completed the entire treatment (Figure 1). The reason for the losses was linked to factors of discontinuity, outlier or adherence to intervention below 80% - assessed by the Morisky Test. The adverse events presented were diarrhea (n = 01) and gastrointestinal discomfort (n = 01).

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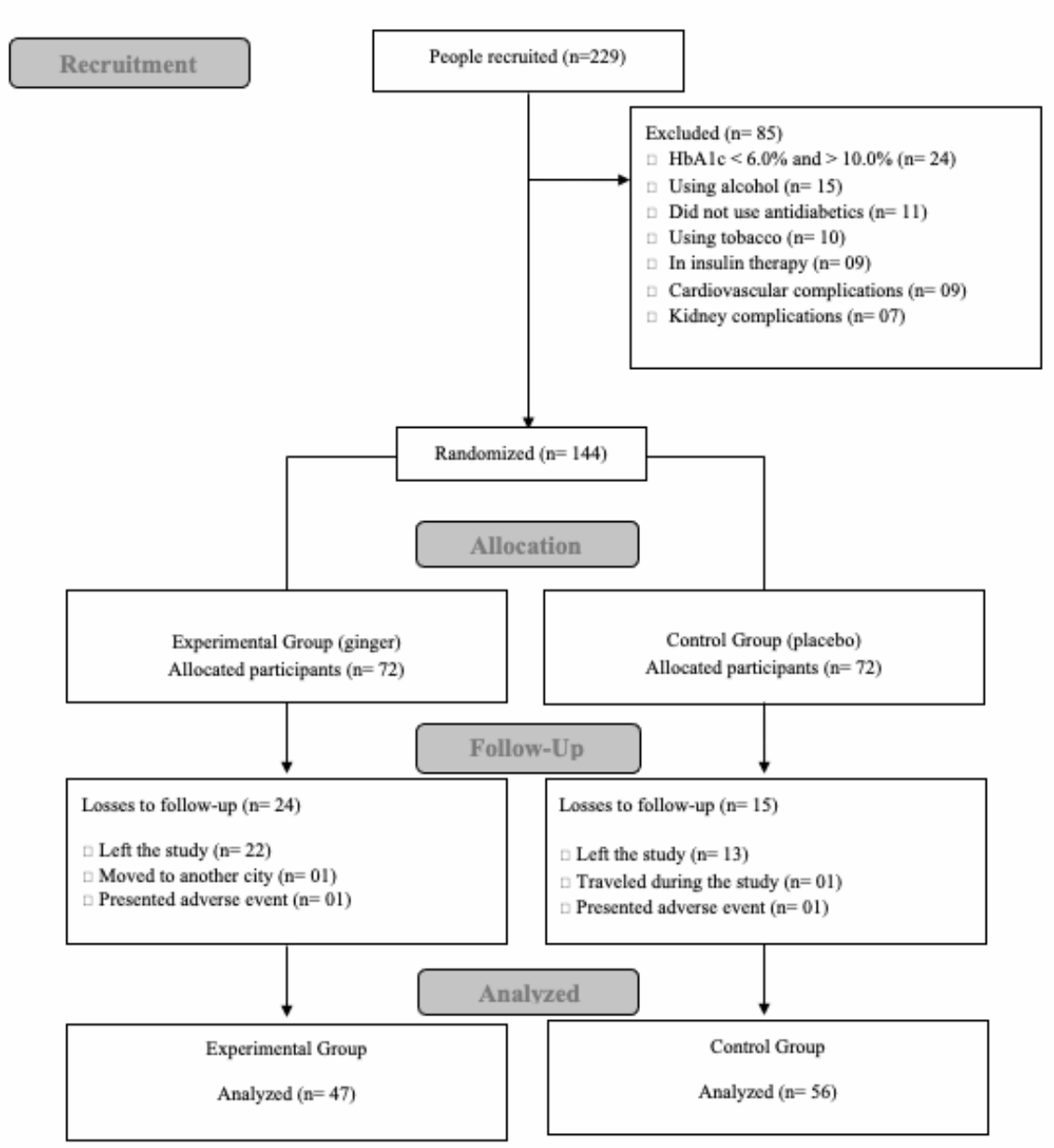
Figure 1 – Flowchart of the study participants



Source: The authors, 2018.

Data analysis and treatment procedures

The data were analyzed by intention to treat. For continuous variables, data were presented on average. In the categorical variables, the data were exposed in frequency and prevalence rate in order to investigate associations between risk factors and disease. Mann-Whitney U test was used to analyze the characteristics of the groups. To verify the behavior of the numerical variables, at both times, the Wilcoxon test was used. A significance level of 5% was adopted. Pearson's chi-square test and Fisher's exact test for categorical variables were used to investigate the association between variables. Statistical analyzes were performed using the

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statistical program Statistical Package for the Social Sciences (SPSS), version 22.0 (USA) and software R 3.3.1. The recorded blood pressure values were adjusted in the analysis.

Ethical aspects

The study was conducted in accordance with Brazilian National Health Council, approved by the Research Ethics Committee, of the State University of Piauí under no. 2,248,450 and registered with the Brazilian Network of Clinical Trials (REBEC) (RBR-2rt2wy / TRIAL: U111-1202-1650).

RESULTS

After 90 days, 103 people completed the study, 47 in the EG and 56 in the CG. Most participants were 58.64 years old (SD = 10.75), were female (69.9%), married (60.1%), lived with their family (88.3%), were brown (54.3%), had completed elementary school (43.6%), were retired (61.1%), had an income of up to R$954.00 brazilian reais (52.4%) - corresponding as US$171 dollars in 2020 November; and belonged to the low socioeconomic class (68.9%).

CG and EG participants were homogeneous in terms of the investigated clinical variables. Most participants had less than five years of diagnosis of T2DM, had a quarterly follow-up, did not practice physical exercise and had hypertension (Table 1).

Table 1 – Characterization of participants according to clinical variables.

Variables	Total (n= 103)	Control Group (n= 56)	Experimental Group (n= 47)	*p-value*
T2DM time				
2 to 5 years	42 (40.8%)	22 (39.3%)	20 (42.6%)	
6 to 10 years	33 (32.0%)	20 (35.7%)	13 (27.7%)	0.670*
> 10 years	28 (27.2%)	14 (25.0%)	14 (29.8%)	
Hypertension				
Yes	62 (60.2%)	31 (55.4%)	31 (66%)	0.274*
Not	41 (39.8%)	25 (44.6%)	16 (34%)	

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Follow-up frequency at BHU				
Monthly	18 (17.5%)	09 (16.1%)	09 (19.1%)	
Quarterly	45 (43.7%)	28 (50.0%)	17 (36.2%)	
Semester	26 (25.2%)	12 (21.4%)	14 (29.8%)	0.558*
Yearly	14 (13.6%)	07 (12.5%)	07 (14.9%)	
Physical exercise				
Before the intervention	38 (35.9%)	21 (37.5%)	17 (36.2%)	0.889**
After the intervention	35 (34.0%)	19 (33.9%)	16 (34.0%)	0.990**

Source: Research data, 2018.

* Pearson's Chi-square test; ** Chi-square test. 95% confidence interval.

When analyzing the BP values, the systolic values of the CG participants remained the same in the post-intervention, and in the EG there was a reduction, although not statistically significant. As for diastolic BP, there was a downward trend in both groups, but also without statistical significance. In the intergroup analysis, however, no outcome variable was significant. It should be noted that the investigated groups were homogeneous in terms of the outcome variables (Table 2).

Table 2 – Intra and intergroup comparison of systolic and diastolic blood pressure values.

Variable	**Control Group (n= 56)**	**Experimental Group (n= 47)**	***p-value***
Systolic blood pressure			
Before the intervention	125 ± 15.93	131 ± 19.99	0.146*
After the intervention	125 ± 14.36	130 ± 18.69	0.147*
p	0.527**	0.870**	
Diastolic blood pressure			
Before the intervention	77 ± 08.90	80 ± 09.47	0.039*

After the intervention	76 ± 09.44	76 ± 14.77	0.937*
p	0.955**	0.066**	

Source: Research data, 2018.

*Mann-Whitney test; **Wilcoxon test for comparison between before and after treatment.

DISCUSSION

The results of this study showed that the use of ginger, in doses of 1.2 g per day, did not reduce blood pressure values in individuals with T2DM. Although most participants were also diagnosed with high blood pressure, and used antihypertensive medications, the herbal medicine did not have enough effect to be indicated as adjuvant therapy.

In our research, there was a higher prevalence of females. Women have a high tendency to accumulate fat, generating pro-inflammatory changes, insulin resistance and, consequently, diabetes[12]. The average age among the participants was 58 years. Evidence has shown that during the aging process, people with diabetes have continuous exposure to hyperglycemia, which can lead to systematic endothelial dysfunction and cardiovascular complications and interfere with blood glucose and blood pressure control[13].

As for the marital situation, we identified a predominance of married people living with the family. Compared to single people, marriage offers an environment of continuous and lasting support, which can promote physical and mental health. Also, frequent contact with family and friends is associated with positive self-care behaviors and adherence to treatment[14].

In this study, more than half of those investigated were retired and had an income below the minimum wage. The etiology of chronic diseases such as T2DM or hypertension, is strongly associated with inappropriate lifestyle habits and stressors resulting from work activity or unemployment. In addition, when poorly controlled, diabetes brings substantial costs to those who have the disease, making care for those with low income unfeasible[3].

Linked to this is the time of diagnosis of the disease. In this survey, more than 40% of the participants had less than five years of diabetes. This fact may be associated with less knowledge about the disease and, consequently, insufficient control of the disease and related comorbidities, such as hypertension[12]. Hypertension was present in more than 60% of the individuals in both groups analyzed (EG and CG), which led us to assess whether ginger had any effect on this variable.

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After the intervention, it is possible to observe a tendency of reduction in the values of systolic and diastolic pressure of the participants who used ginger, although not significant, not allowing the indication of the therapy. Similar outcomes have also been found in clinical trials developed in other countries[9,15]. Corroborating the findings, a systematic review that investigated the effect of different herbal medicines used for therapeutic purposes did not identify antihypertensive components in ginger[7].

However, the literature is not unanimous, and a study who researched the effect of ginger powder supplementation on blood pressure in patients with DM2, observed a significant decrease in blood pressure systolic and diastolic, as well as the pulse pressure and average BP, indicating that daily consumption of 3 g capsules ginger powder for 8 weeks brings improvements to blood pressure in patients with DM2[8].

In this perspective, a systematic review with meta-analysis pointed out that supplementation with ginger presents favorable results in blood pressure, being able to reduce systolic and diastolic BP with significance only in investigations with individuals aged ≤50 years, with 8 ≤ weeks of research and doses of ginger ≥3 g daily [16].

This hypotensive effect of ginger may be related to its ability to inhibit the Angiotensin-1-converting Enzyme (ACE), potent vasodilator that plays an important role in the development of hypertension[17]. Thus, being considered a new angiotensin II type 1 receptor antagonist, it inhibits ACE by lowering blood pressure. In addition, it may also be associated with platelet hyperactivity and potential neuroprotective effects[17-18].

Ginger can still be used in an associated with antihypertensive drugs, playing an adjunct role in the treatment of hypertension, providing an additional effect[18]. However, such results present us with a still limited scenario, which does not allow to expand discussions on the subject and point to the need for further investigations in the area.

In this context, Nursing in Advanced Practices has shown great potential for the treatment of people with chronic diseases by all the innovative practices introduced in recent years[19]. Being at the forefront of care for chronic patients, nurses must assume leadership roles and use research such as this to maximize clinical performance in places such as Primary Health Care, through comprehensive and resolving interventions[20].

This study is unprecedented in the country and sought to fill gaps in the literature about the role of ginger in reducing blood pressure in people with T2DM. Although without statistically positive outcomes, this clinical trial can increase the knowledge of health professionals about the use of this CAM in the management of diseases such as diabetes.

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We consider that our research had as main limitations the intervention time and the dose of ginger offered. Despite the fact that most of the existing research on the subject has carried out interventions for 90 days, we believe that a longer follow-up period would allow a better assessment of the outcome drawn. As adverse events, one participant in the CG and another in the EG experienced episodes of nausea and diarrhea, respectively.

CONCLUSION

The results of this study show that ginger, at doses of 1.2 g/day, did not have the potential to reduce blood pressure in people with T2DM. It is suggested that future investigations expand the dose and the intervention period and explore the cost-effectiveness of the herbal medicine to subsidize its insertion in the Brazilian health system.

Regarding nursing practice, health promotion strategies are essential for the prevention of chronic diseases. In this context, advanced disease maintenance and control practices, such as those in this study, are necessary for successful care science. The findings suggest that nursing professionals should take up research in order to increase the scope of resources to be included in their care plan, as well as in investigating tools to prevent or slow the advance of diseases such as diabetes and hypertension.

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