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Effectiveness of strategies for nutritional therapy for patients with type 2 diabetes and/or hypertension in primary care: protocol of a systematic review of randomised controlled trials

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ABSTRACT

Introduction Despite the increasing number of drugs available and various guidelines on the management of type 2 diabetes mellitus (T2DM) and hypertension, an expressive number of patients continue with these diseases uncontrolled. Nutrition therapy (NT) plays a fundamental role in the prevention and management of these comorbidities, as well as in the prevention of complications related to them. The objective of this review is to evaluate the effectiveness of NT strategies in the management of patients with T2DM and/or hypertension in primary care. The selected strategies did not substitute pharmaceutical treatment but instead focused on preventing a sedentary lifestyle and stimulating healthy nutrition.

Methods and analysis We will perform a systematic review according to Cochrane methodology of randomised controlled trials, wherein patients with T2DM and/or hypertension were allocated into one of the two groups: NT strategy, which may be of dietary quality or energy restriction, and conventional treatment. The primary outcomes will be glycaemic and blood pressure (BP) control, measured by final glycosylated hemoglobin (HbA1c) (%) and BP (mm Hg), respectively. Four general and adaptive search strategies have been created for the Embase, Medline, Latin American and Caribbean Health Sciences Literature (LILACS) and Cochrane Central Register of Controlled Trials (CENTRAL) electronic databases. Two reviewers will independently select eligible studies, assess the risk of bias and extract data from the included studies. Similar outcomes measured in at least two trials will be plotted in the meta-analysis using Review Manager V.5.3. The quality of evidence of the effect estimate of the intervention will be generated according to the Grading of Recommendations Assessment, Development, and Evaluation Working Group.

Ethics and dissemination As no primary data collection will be undertaken, formal ethical assessment is not required. We plan to present the results of this systematic review in a peer-reviewed scientific journal, conferences and the popular press.

PROSPERO registration number Our systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on 20 December 2018 (Registration number CRD42018118117).

Strengths and limitations of this study

- ► Trial eligibility evaluation, risk of bias assessment, as well as data excretion will be performed in teams of reviewers, independently and in pairs.
- ► We will apply the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach to evaluate our confidence in the effect estimates of each intervention.
- ► The potential causes of heterogeneity between studies have been anticipated, and will be evaluated by subgroup analysis.
- ► As the primary outcomes selected are surrogate endpoints, the quality of evidence according to the GRADE approach will be probably low.
- ► Variability in effect estimates is expected among the different interventions.

INTRODUCTION

Diabetes mellitus (DM) and hypertension may lead to cardiovascular diseases and in some cases death. These chronic diseases have a major economic impact since they reduce work productivity and, consequently, family income. Such loss was estimated at US$4.18 billion from 2006 to 2015.[1]

In 2015, the International Diabetes Federation (IDF) estimated that 8.8% (uncertainty interval: 7.2–11.4) of the world population aged between 20 and 79 (including 415 million people) lived with diabetes and 5.0 million deaths were attributable to diabetes.[2] For 2040, the IDF has estimated that 642 million adult people (uncertainty interval: 521–829 million) will have diabetes (global estimate prevalence of 10.4%).[2]

Type 2 diabetes mellitus (T2DM) accounts for 90%–95% of all cases of diabetes, and usually affects individuals from the fourth decade of life, although in some countries there is an increase in its incidence in children and young people.[3]

The most relevant risk factor for complications related to T2DM is inadequate glycaemic control.[4] The United Kingdom Prospective Diabetes Study demonstrated that in patients with T2DM an intensive blood glucose control, a median HbA1C level of 7.0% in comparison with a median level of 7.9%, was associated with a significant reduction in the incidence of microvascular complications.[5]

A systematic analysis of global health disparities in hypertension estimated that in 2010 the worldwide prevalence of hypertension was 1.39 billion persons, representing 31% of all adults (95% CI 30.0% to 32.2%). From 2000 to 2010, the age-standardised prevalence of hypertension decreased by 2.6% in high-income countries but increased by 7.7% in low-income and middle-income countries.[6]

The Framingham study demonstrated that blood pressure (BP) is a predictor of coronary artery disease, stroke, transient ischaemic attack and congestive heart failure.[7] In 2001, approximately 7.6 million deaths worldwide were attributed to an increase in BP, 54% to stroke and 47% to coronary artery disease.[8]

Despite the increasing number of drugs available and various guidelines on the management of these chronic diseases, an expressive number of patients continue with the disease uncontrolled. In a multicentre, cross-sectional, epidemiological, questionnaire-based study conducted in nine Latin American countries, 56.8% of patients with T2DM had poor glycaemic control (HbA1c≥7%).[9] The highest prevalence of unsuccessful treatment was in Peru, where only 7.5% achieved metabolic and BP levels as recommended by the American Diabetes Association (ADA).[10] In 2010, only 13.8% of adults with hypertension had their BP controlled worldwide.[6]

This discrepancy is due to knowledge gaps together with the management of these individuals.[11] Despite the necessity for multidisciplinary teams, the health services are mostly physician centred.

Nutrition therapy (NT) consists of education and support to help patients adopt healthy eating pattern, and in diabetes and hypertension, it plays a fundamental role in the prevention and management of these comorbidities, as well as in the prevention of complications related to them.[12–14]

A consensus report by the ADA and the European Association for the Study of Diabetes recommends that an individualised programme of NT be offered to all patients with T2DM.[14] The dimensions of the NT include dietary quality and energy restriction. There is no single ratio of carbohydrate, proteins and fat intake which fits all the requirements of patients with T2DM.[14] Therefore, recommendation is to combine patient preference and metabolic needs with healthy dietary habits that are feasible and sustainable.[14]

Regarding dietary quality, NT that may guide individualised treatment choices in adults with T2DM is Mediterranean diet, the Dietary Approaches to Stop Hypertension (DASH), low carbohydrate and vegetarian.[14] The DASH and Mediterranean diets also result in BP reduction.[15]

A network meta-analysis on the comparative efficacy of different dietary approaches in patients with T2DM showed that all dietary approaches significantly reduced HbA1c (−0.82% to −0.47% reduction) and fasting glucose (−1.61 to −1.00 mmol/L reduction) compared with control diet. However, the Mediterranean diet was the most effective to improve glycaemic control.[16]

For non-surgical energy restriction, the main choices are individual energy restriction, counselling programme and food substitution programme. The most effective strategies for weight reduction involve food substitution and an intensive and a sustained counselling programme.[14]

Although several randomised trials have evaluated the effectiveness of NT in the management of diabetes and hypertension,[17–20] no systematic reviews were found that met the eligibility criteria described below.

The objective of this review is to evaluate the effectiveness of NT strategies in the management of patients with T2DM and/or hypertension in primary care. The selected strategies did not substitute pharmaceutical treatment but instead focused on preventing a sedentary lifestyle and stimulating healthy nutrition.

METHODS AND ANALYSIS

This systematic review will be conducted according to the Cochrane Collaboration[21] and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement.[22] This protocol contains the 17 items considered to be essential in a systematic review according to the PRISMA Protocols.[23]

Patient and public involvement

We did not directly include patient in this study, but during the protocol development, priority of the research question, and type of intervention were informed by discussions with members of the Brazilian Health Ministry choice of outcome measures, which identified this research as being a priority area for managing patients with T2DM and/or hypertension in primary care.

Eligibility criteria

The selected randomised controlled trials will meet the 'PICO' structure described next:

Participants (P)

Adults, regardless of gender, over 18 years of age, diagnosed with T2DM and/or hypertension. The diagnosis of DM should have been established according to ADA criteria: fasting glycaemia greater than or equal to 126 mg/dL; glycaemia above 200 mg/dL associated with classic DM symptoms; glycaemia 2 hours after overload with 75

g of glucose greater than or equal to 200 mg/dL; HbA1c greater than or equal to 6.5%.[24] Subjects will be classified as T2DM if there is a lack of insulin in the diagnosis, associated with the presence of at least one of the following factors: obesity, overweight, increased waist circumference or clinical signs of insulin resistance. Hypertension is a clinical condition characterised by persistent systolic BP ≥140 mm Hg and/or diastolic BP ≥90 mm Hg.[25]

Types of interventions (I)

We will consider as intervention pharmacological treatment for T2DM and/or hypertension associated to a NT strategy that was performed in primary care, focused on stimulating healthy nutrition, and with minimum period of 4 months. The NT may be of dietary quality or energy restriction, which include (1) Mediterranean diet, (2) DASH diet,[15] (3) low carbohydrate diet,[26] (4) vegetarian diet,[27] (5) low glycaemic index diet,[28] (6) high protein diet,[29] (7) others nutrition plans implemented by a nutritionist, with recommendations for life style changes, and strategies to reduce calories and dietary fat,[30] (8) nutrition counselling programme[31] and (9) food substitution programme followed by gradual reintroduction of meals.[32] The nutrition counselling programme can be conducted by nutritionists, physical educators, nurses, psychologists, educators in diabetics, physicians, and so on.

Comparison (C)

The comparison group will be the conventional treatment of diabetes and/or hypertension, including drug treatment associated with a general orientation regarding healthy nutrition. An episodic evaluation with a nutritionist, nurse, physical trainer or educator in diabetes, which provides a general orientation regarding changes in lifestyle, will be considered conventional treatment if the patients are not provided with subsequent follow-up.

Exclusion criteria

We will exclude trials whose interventions were exclusively based on dietary supplements, trials conducted in other scenarios than primary care, trials including pregnant women or patients with secondary hypertension, trials with a cointervention that was not applied in intervention and control group, and diets based on day calories less than 600 kcal (very low energy diets).

Outcomes (O)

The primary outcomes will be glycaemic and BP control, measured by final HbA1c (%) and BP (mm Hg), respectively. The secondary outcomes will be frequency of cardiovascular events (acute myocardial infarction, cerebral vascular accident), weight loss (measured by final weight or body mass index (BMI)) and death.

Time of outcome evaluation

The outcomes will be evaluated at 6, 12 and more than 12 months. Trials with outcomes within these timepoints will be combined with the closest timepoint.

Identification of studies

Electronic databases

Four general research strategies will be applied to the main electronic health databases: Embase (Elsevier, 1980–2019), Medline (PubMed, 1966–2019) and LILACS (Virtual Health Library, 1982–2019) of Controlled Clinical Trials of the Cochrane Collaboration (CENTRAL—Cochrane). The search strategies will contain descriptors and synonyms of T2DM, primary health care, hypertension, nutrition and lifestyle. PubMed will use the filter for randomised studies, as supported by Cochrane and the embedded filter will be used for the same purpose in Embase. There will be no language or year restrictions. A draft of the Medline search strategy is also included in online Supplementary Data.

The following databases will also be searched for eligible studies: Trip database, SCOPUS, Web of Science, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Australasian Medical Index, and Chinese Biomedical Literature Database. We will also search for studies on ClinicalTrials.gov, the Brazilian Registry of Clinical Trials (Rebec) and the grey literature, through abstracts published in annals and lectures.

References of relevant primary or secondary studies will be searched in order to identify additional eligible studies. Endnote citation management software will be used to download references and remove duplicate entries. The initial screening of abstracts and titles will be performed using the software Rayyan QCRI.

DATA COLLECTION AND ANALYSIS

Study selection

Two reviewers (RGOFL and JSCG) will independently select potentially eligible studies for inclusion in the review based on the titles and abstracts. The studies selected for full-text review will be subsequently assessed for adequacy to the proposed PICO. In case of disagreement, there will be a consensus meeting between the reviewers and the project coordinator (VdSN-N) for a final decision.

Data extraction and management

Both reviewers will use a standard form to extract the following data from the selected studies: year of publication, country, sample size, follow-up time, information regarding eligibility criteria (inclusion and exclusion criteria), type of intervention and control, outcomes and risk of bias. Baseline characteristics of the sample (age, gender, weight, BMI, waist circumference, time from diagnosis of T2DM and/or hypertension, glycaemic and/or pressure control prior to the study, medications in use and presence of chronic complications related to diabetes and/or hypertension) and outcome results will also be collected.

To ensure consistency between reviewers, we will perform a calibration exercise before beginning the review. In the case of duplicate publications or multiple reports from the primary study, data extraction will be

optimised using the best information available for all items in the same study. There will be a discussion between the reviewers and VdSN-N in case of disagreements.

Assessment of bias risk in the included studies

For selected clinical trials, the risk of bias will be assessed according to the criteria described in the Cochrane Handbook for Systematic Reviews of Interventions,[21] which considers the following seven areas: randomisation process, allocation concealment, blinding of participants and investigators, blinding of evaluators to the outcome, loss of patients to follow-up and intention-to-treat analysis, selective outcome reporting and other biases. For each domain, two reviewers will assign a low, high or indeterminate risk of bias. In case of disagreement, there will be a discussion between the reviewers and VdSN-N before the final classification.

Measurement of treatment effect

For dichotomous data, the relative risk will be calculated with 95% CIs as the estimate of the intervention effect. Continuous data will be expressed as means and SD and the differences between means with 95% CIs will be used as an estimate of intervention effect.

Unit of analysis

The unit of analysis will be the data published in the included studies. In the case of crossover studies, only data from the first phase will be considered. For cluster studies, the unit of analysis will be the patients.

Lack of data

The authors of the original studies will be contacted, if necessary, to obtain missing data. We will use the data available in published articles provided by their authors or registration platforms. If available, we will preferentially use data from intention-to-treat analysis.

Evaluation of publication bias

If more than 10 trials are included in the meta-analysis of a specific outcome, we will use funnel plots to investigate the presence of publication bias.[33] An asymmetry may indicate the presence of such bias, in which case Egger regression tests will be applied.[33]

Data synthesis

Similar outcomes in at least two studies will be plotted in the meta-analysis using Review Manager V.5.3 (Review Manager. [RevMan], version 5.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). A random-effect model will be used for the meta-analysis. If quantitative synthesis is not appropriate, a narrative synthesis will be provided.

Sensitivity analysis

If possible, we plan to perform a sensitivity analysis by evaluating by subgroup the studies with high and low risks of selection and attrition biases.

Subgroup analysis

If enough data are available, subgroup analyses will be performed according to patient diagnosis (diabetes only, hypertension only or both), ethnicity (African origin, Mongoloid, Caucasian), trial size (trials>100 patients vs trials<100 patients), stage of hypertension and/or diabetes, type of intervention and time of follow-up (6, 12 and more than 12 months).

Heterogeneity assessment

Inconsistencies between the results of the included studies will be ascertained by visual inspection of forest plots (no overlap of CIs around the effect estimates of the individual studies) and by Higgins or I^2 statistic, in which I^2 >50% indicates a moderate probability of heterogeneity, and by χ^2 tests, where p<0.10 indicates heterogeneity. The potential causes of heterogeneity between studies will be evaluated by subgroup analysis. If the inconsistency was not explained by subgroup analysis, and more than 10 trials are included in the meta-analysis, a meta-regression using the metareg command available for the Stata statistical package will be performed.

Quality of evidence

The quality of the evidence of the intervention's effect estimate will be assessed according to the Grading of Recommendations Assessment, Development, and Evaluation methodological guidelines.[34]

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Contributors VdSN-N is the guarantor of the review. All authors developed the systematic review protocol; the manuscript protocol was drafted by VdSN-N and revised by RGOFL, JSCG and ALM. VdSN-N has developed the search strategies. All authors will independently screen the eligible studies, extract data from included studies and assess the risk of bias. VdSN-N will elaborate the standard extract form. VdSN-N will supervise all phases of this review and referee any disagreement to avoid any errors. All authors will participate of data synthesis and quality of evidence. All authors critically revised the manuscript and approved the final version.

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