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Nutritional therapy in amyotrophic lateral sclerosis: Protocol for a systematic review and meta-analysis

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Keywords:	NUTRITION & DIETETICS, Neuromuscular disease < NEUROLOGY, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

ABSTRACT

Introduction: Amyotrophic Lateral Sclerosis (ALS) is a complex neurodegenerative disease characterized by the degeneration of motor neurons. Nutritional interventions in ALS are essential and must be based on scientific evidence to provide quality of health care, improve the quality of life, and increase survival time. Therefore, this protocol of systematic reviews and meta-analyses aims to present a synthesis of evidence-based recommendations to support adequate nutrition therapy for patients with ALS.

Methods and analysis: The search will be performed using the following databases: PubMed, Excerpta Medica Database (Embase), Scopus, SciELO, Web of Science, LILACS, Cochrane Central Register of Controlled Trials (CENTRAL), ScienceDirect, ProQuest, and Google Scholar. We will include clinical practice guidelines, treatment protocols, systematic reviews, and clinical trials according to the three research questions to be answered related to nutrition therapy and interventions in ALS patients. This protocol will be developed in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P). To evaluate the methodological quality of the studies, AGREE II, Cochrane Risk of Bias (RoB 2.0), and ROBINS-I tools will be used. In addition, The Grading of Recommendations Assessment, Development and Evaluation (short GRADE) will be used to assess the quality of evidence and the strength of the recommendations. The findings will be summarized and presented descriptively according to the Cochrane Collaboration Handbook and the standard statistical meta-analysis techniques.

Ethics and dissemination: Ethical approval and human consent are not required because this is a protocol for systematic review and only secondary data will be used. Findings will be published in a peer-reviewed journal and presented at conferences. In case of any changes in this protocol,

amendments will be updated in PROSPERO and the modifications will be explained in the final report of this review.

PROSPERO registration number: CRD42021233088.

Keywords: amyotrophic lateral sclerosis, nutrition therapy, quality of health care

Strengths and limitations of this study:

- In this study a synthesis of evidence-based recommendations to support adequate nutrition therapy in ALS will be provided.
- This protocol encompasses two systematic reviews and adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement guidelines.
- No restrictions of time and language will be applied in our search.
- The methodological quality of the studies will be performed using the AGREE II statement.
- For the methodological quality and risk of bias of clinical trials will be accomplished using the Cochrane Risk of Bias (RoB 2.0) and ROBINS-I tools for randomized and non-randomized studies, respectively.
- Meta-analysis may not be possible for certain outcomes due to a limited number of eligible studies.

INTRODUCTION

ALS is a multisystemic neurodegenerative disease characterized by progressive cell death of upper and lower motor neurons.[1, 2] Worldwide ALS prevalence varies from 1.57 cases per

100,000 to 9.62 per 100,000. Its incidence varies from 0.42 per 100,000 to 2.76 per 100,000 people/year. Both ALS prevalence and incidence are higher in developed regions.[3] Clinical signs of the disease have a low incidence before age 50 years, with a peak around age 85 years followed by a marked decrease in incidence. However, the onset of this disease is rarely possible in early adulthood.[4] The severity of the disease points to a short median survival of 3 to 4 years after the initial diagnosis.[5-8]

Malnutrition is a frequent condition in patients with ALS, with prevalence ranging from 16 to 53%.[9] The Body Mass Index (BMI) is an important anthropometric parameter for diagnosing malnutrition among these patients. BMI reduction is related to faster disease progression and increased risk of mortality.[10] Marin et al.[11] demonstrated that 5% of body weight loss increases the risk of death by 30% in patients with ALS. Thus, nutritional care is essential for maintaining adequate nutritional status, which positively affects these patients' functional capacity, quality of life, and survival time.[12-14]

Several risk factors such as dysphagia, anorexia, gastrointestinal disorders, cognitive impairment, apathy, psychological disorders, and inadequate energy and nutrient intake contribute to malnutrition in patients with ALS. In addition, hypermetabolism may be present and can increase the risk of malnutrition or aggravate this condition, especially in the absence of nutritional care.[15, 16] Therefore, evidence-based nutritional interventions for ALS are of the utmost importance and must consider the different stages of the disease.[17]

Clinical Practice Guidelines (CPGs) have been developed to provide scientific evidence to support clinical decision-making of health professionals and establish standards of care for many conditions.[18, 19] CPGs focused on all aspects of nutritional therapy for ALS are still lacking. Existent guidelines on this matter only address some nutritional aspects, most of them related to

gastrostomy and dysphagia. Many other aspects of nutritional therapy have not been covered, such as energy and nutrient requirements, modified consistency diet, micronutrients and bioactive compounds supplementation, and nutrition advice for comorbidities in ALS patients.

Considering this gap and aiming to provide broader guidance on nutrition therapy for ALS patients, it is essential to gather and synthesize recommendations on this subject, based on available scientific evidence of clinical protocols and guidelines. Also, based on the effectiveness of nutritional interventions verified through clinical trials. We believe that a synthesis of recommendations on nutrition therapy in ALS will help and guide the nutrition care process and benefit the patients.[20, 21]

Given the information above, this protocol will seek to answer the following questions: **RQ1** - What are the evidence-based nutritional recommendations to maintain or restore the nutritional status of patients with ALS? **RQ2** - What is the effect of a diet rich in energy and protein in people with ALS? **RQ3** - What are the effects of supplementing isolated micronutrients or bioactive compounds in people with ALS?

Therefore, this protocol aims to build an outline of upcoming systematic reviews and meta-analyses to present a synthesis of evidence-based recommendations to support adequate nutrition therapy and improve the nutritional status of patients with ALS.

METHODS AND ANALYSIS

Protocol Registration

This protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO) database on April 12, 2021 (CRD42021233088). This protocol is in line with international ethical parameters and because it is a study with secondary data, there is no need to

seek approval from a research ethics committee. Also, it was developed in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P) statement guidelines.[22] The PRISMA-P checklist used to prepare this protocol has been provided as an online supplemental file. To report the systematic review, the PRISMA statement with a 27-item checklist and descriptive flow diagram will be used.[23] This present protocol encompasses two systematic reviews and meta-analyses. The first one will be a review of protocols/guidelines aimed to answer the RQ1. The second one will be a review of clinical trials aimed to answer RQ2 and RQ3. The information regarding methods and analysis are described according to the research questions.

Selection Criteria

For RQ1, we will include CPGs, treatment protocols, and systematic reviews. For RQ2 and RQ3, we will only include clinical trials with control groups.

Participants

For all RQ's we will include studies comprised of adults (aged 18 and over) and seniors of both sexes with a clinical diagnosis of ALS as defined, probable, or possible.

Types of interventions

For RQ1, we will include studies involving nutrition therapy recommendations to maintain or restore the nutritional status of patients with ALS. For RQ2, we will include studies implementing a diet rich in energy and/or protein as an intervention. For RQ3, we will include studies supplementing single micronutrients or bioactive compounds as an intervention.

Outcomes measures

For RQ1, only the summary of the recommendations will be performed, with no outcomes to be measured. For the RQ2, the outcome will be the change of body mass index, percentage of weight loss, progression rate of total revised ALS Functional Rating Scale (ALSFRS-R), and mortality rate. For the RQ3, the outcome will be the antioxidant effect, ALSFRS-R progression rate, and mortality rate.

Exclusion Criteria

For all RQ's we will exclude studies with other neurodegenerative diseases or without nutritional recommendations. No restrictions of time and language will be applied in our search.

Search strategy

A comprehensive electronic search will be performed in the following databases: PubMed, Excerpta Medica Database (Embase), Scopus, SciELO, Web of Science, LILACS, Cochrane Central Register of Controlled Trials (CENTRAL), ScienceDirect, ProQuest, and Google Scholar. The search strategy will include the following descriptors (MeSH): “Amyotrophic Lateral Sclerosis”, “Motor Neuron Disease”, “Nutrition”, “Nutritional Assessment”, “Nutrition Therapy”, “Diet”, “Dietary Supplements”, “Deglutition Disorders”, “Guideline”, and “Clinical Protocols”. In addition, the EMTREE terms “Diet Therapy”, “Dysphagia”, and “Practice Guideline” will be included for the Embase database. A draft of our search strategy has been provided as an online supplemental file.

Searches of other resources

To ensure the comprehensiveness of this research, we will supplement searches by hand-searching in the reference lists of retrieved studies or relevant reviews. To identify unpublished studies and assess publication bias, we will also examine *ClinicalTrials.gov* and *ensaiosclinicos.gov.br* for registered clinical trials using interventions such as high-energy and/or high-protein diet and supplementation of micronutrients or bioactive compounds in people with ALS.

Study selection

For all identified studies, at least 2 authors (MDCV and LLL) will independently select and review titles and abstracts using the Rayyan QCRI® tool. Papers that meet the inclusion criteria will be ordered for a full review. Any disagreement will be resolved by discussion with a third reviewer (SHLV). A manual search will be performed if any relevant studies are found using the defined search strategies. All investigators will then review the full text of all eligible studies. The information on the phases of the selection process will be described through PRISMA flow diagram.[23]

Data extraction

The data extraction will be done in a standardized way, using Microsoft Excel by 2 independent authors (MDCV and LLL). Discrepancies between the data extraction will be resolved by consensus. The study characteristics will be collated according to the research questions. For RQ1, the following data will be extracted: general information about the guideline (title, responsible organization, year of publication, and funding); nutritional recommendations

addressed; and the stratification of the level of evidence used. For RQ2 and RQ3, the following data will be extracted: general information (title, authors, journal, year, country); study characteristics (study design, study duration); sample characteristics (sample size, mean age, ALS subtype, ALSFRS-R); intervention (type of intervention, duration, diet characteristics, energy and/or protein amount); outcomes (changes in body mass index, percentage of weight loss, progression rate of functional status, mortality rate); and statistical results. If study reports are incomplete or missing data, corresponding authors will be contacted. If we do not receive clarification, the requested data will be excluded from our analysis and will be commented in the Discussion section.

Evaluation of methodological quality

Two independent authors (SHLV and MDCV) will evaluate the methodological quality of the studies using the AGREE II statement. This instrument assesses six domains: 1. Scope and purpose, 2. Stakeholder involvement, 3. Rigour of development, 4. Clarity of presentation, 5. Applicability, and 6. Editorial independence.[24] To assess the methodological quality and risk of bias of clinical trials, the Cochrane Risk of Bias (RoB 2.0) and ROBINS-I tools will be used for randomized and non-randomized studies, respectively.[25, 26]

Data synthesis

For the first systematic review (RQ1), the findings and main recommendations will be narratively summarized. For the second systematic review (RQ2 and RQ3), meta-analysis will be performed, if possible. If meta-analysis is not possible, we will conduct a systematic review with narrative analysis tabling the results.

Assessment of heterogeneity

To assess the heterogeneity, we plan to calculate the standard chi-square statistic, which is a quantitative measure of inconsistency between the studies. Next, the I^2 index will be calculated to quantify heterogeneity. The I^2 statistic describes the percentage of variation across studies due to heterogeneity rather than chance. No heterogeneity is observed when I^2 is 0%, and the variability can be explained by chance alone. A value of I^2 >50% indicates high heterogeneity.

Meta-analysis

If there is the possibility of meta-analysis, standard statistical techniques will be used. If I^2 value is <50% and p-value is >0.05, the fixed effect model will be chosen. If I^2 is <50% or p-value is <0.05, the random effect model will be used to combine the tests to calculate relative risk (RR) and 95% CI using the DerSimonian-Laird method. If substantial heterogeneity occurs, we will perform subgroup analysis and meta-regression to explore the source of heterogeneity. Publication bias will be assessed using a funnel plot and its asymmetry will be verified by linear regression.

Subgroup analysis

For the RQ1 the analysis of subgroups is not applicable. If sufficient data are available for the RQ2 and RQ3, the subgroup analysis will consider disease onset (bulbar or spinal), age of onset, disease duration, and disease stages (early, middle, late, and end).

Assessment of quality of evidence (GRADE)

Two independent authors (MDCV and LLL) will assess the quality of the evidence and the strength of the recommendations provided by the selected studies. For this purpose, we will use the Grading of Recommendations, Assessment, Development and Evaluation (GRADE)[27] for decision-making in health, which classifies the quality of evidence into four levels (high, moderate, low, and very low) and the strength of the evidence into two levels (strong or weak).

Patient and public involvement

No patients or the public will be directly engaged in this research, as it is conducted using secondary data.

DISCUSSION

This study aims to gather and synthesize recommendations for nutritional intervention and treatment based on available scientific evidence from clinical protocols and guidelines. Also, the effectiveness of interventions will be verified through clinical trials.

Weight loss, low BMI, and malnutrition are frequent in ALS patients. According to the guideline conducted by Burgos et al.,[28] the BMI reduction in ALS patients is associated with shortened survival and high risk of mortality.

A systematic review states that there is no cure or effective treatment for ALS to date. Multidisciplinary care is the basis for its treatment, including nutritional support as well as respiratory and symptom management during the disease. Furthermore, the review highlights that dietary intervention can help to improve nutrition status. For example, gastrostomy is indicated if oral intake is insufficient or is no longer safe.[29]

Dorst et al. found that high-energy supplementation effectively stabilizes the body weight of patients with ALS and no side effects were detected. The authors also observed a positive impact on the survival of the patients. Thus, the use of high-energy supplementation was suggested.[30] In a cohort study, Traynor et al.[31] demonstrated that ALS patients who received multidisciplinary care had a better prognosis than patients who received general care through a neurology clinic.

Scientific entities specialized in ALS recognize nutrition as integral part of care during the course of the disease and address some nutritional recommendations.[32, 33] Nutrition therapy seeks to prevent malnutrition, maintain adequate nutritional status, promote hemodynamic stability, reduce the rate of disease progression, and positively impact the quality of life and survival of ALS patients.[34] Thus, identifying consistent recommendations for nutrition intervention in ALS is of the utmost importance and will contribute to more assertive patient care.[35-38] Nevertheless, systematic reviews and guidelines about ALS nutritional therapy are scarce and some of them present gaps because they do not discuss specific aspects regarding nutritional treatment and management that should be implemented in this type of patient.

For example, the recommendations by Garcia et al.[39] describe the nutritional aspects of ALS and nutritional management with recommendations for high energy intake and those related to enteral and parenteral nutrition. However, it does not address percentages of macronutrients distribution, micronutrients requirements, or adjuvant nutritional supplements.

In a review paper about nutrition management in ALS, Greenwood et al.[37] prioritize the quantitative recommendation of protein but do not determine recommendations for lipids, carbohydrates, fibers, micronutrients, bioactive compounds, and nutritional supplements. The pieces of information we gathered show how these two systematic reviews proposed by our

group are needed and can be helpful in assisting the nutrition care of ALS patients with robust recommendations based on scientific evidence.

In this sense, the development of updated systematic reviews with meta-analyses and synthesized recommendations on nutrition therapy of patients with ALS can reduce the nutritional risk and positively influence their quality of life and survival time. Furthermore, it will support the first Brazilian guideline of nutrition therapy in ALS, which will guide the clinical nutrition practice with greater safety and efficiency. Thus, we believe this protocol is relevant and it will benefit the scientific community, health care professionals, caregivers, and especially patients with ALS. In addition, the systematic reviews proposed can also help to highlight areas that require more research in the subject of nutrition therapy and ALS.

ETHICS AND DISSEMINATION

Ethical approval and human consent are not required because this is a protocol for systematic review and only secondary data will be used. Findings will be published in a peer-reviewed journal and presented at conferences. In case of any changes in this protocol, amendments will be updated in PROSPERO and explanations of these modifications will be described in the final report of this review.

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CONTRIBUTORS

MDCV, LLL, and GP conceptualized and designed the protocol. The protocol manuscript was written by MDCV and LLL. It was critically reviewed by GP, GCBSM, KMDC, SHLV, and JBN. The search strategy was developed by MDCV, LLL, SHLV, GP, and GCBSM. MDCV, KMDC, and LLL will lead the study selection. MDCV, LLL, and KMDC will be responsible for data extraction. Statistical analysis will be performed by MDCV, SHLV, LLL, GCBSM, and GP. JBN will be the third party and will host consensus meetings at each stage in case of disagreement. All authors read, reviewed, and approved the final protocol.

FUNDING

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COMPETING INTERESTS

None declared.

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388 amyotrophic lateral sclerosis: summary of recommendations]. *Nutr Hosp* 2018;35(5):1243-
389 1251.

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	X		OK*
Update	1b	If the protocol is for an update of a previous systematic review, identify as such		X	NA
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	X		26
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	X		OK*
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	X		277-284
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments		X	NA
Support					
Sources	5a	Indicate sources of financial or other support for the review	X		286-290
Sponsor	5b	Provide name for the review funder and/or sponsor	X		286-290
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol		X	NA
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	X		58-73
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	X		74-76
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	X		104-127

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	X		104-127
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	X		129-146
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	X		148-158
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	X		148-155
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	X		157-160; 168-171
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	X		161-168
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	X		161-168
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	X		173-179
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	X		181-185
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	X		187-201
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	X		203-206
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	X		182-185
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	X		200-201
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	X		208-213

* The title is included in the Step 1 of the submission process at BMJ Open's author dashboard. The title is in accordance with PRISMA-P recommendations.

Supplemental Material [Draff of Search Strategy]

Database		Equations
PubMed	1	"amyotrophic lateral sclerosis" OR "motor neuron disease" AND "nutrition" AND "guideline"
	2	“amyotrophic lateral sclerosis” OR “motor neuron disease” AND “nutrition therapy” AND “dietary supplements”

BMJ Open

Nutritional therapy in amyotrophic lateral sclerosis: Protocol for a systematic review and meta-analysis

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Nutritional therapy in amyotrophic lateral sclerosis: Protocol for a systematic review and meta-analysis

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Keywords: amyotrophic lateral sclerosis, nutrition therapy, quality of health care

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ABSTRACT

Introduction: Amyotrophic Lateral Sclerosis (ALS) is a complex neurodegenerative disease characterized by the degeneration of motor neurons. Nutritional interventions in ALS are essential and must be based on scientific evidence to provide quality of health care, improve the quality of life, and increase survival time. Therefore, this protocol of systematic reviews and meta-analyses aims to present a synthesis of evidence-based recommendations to support adequate nutrition therapy for patients with ALS.

Methods and analysis: The search will be performed using the following databases: PubMed, Excerpta Medica Database (Embase), Scopus, SciELO, Web of Science, LILACS, Cochrane Central Register of Controlled Trials (CENTRAL), ScienceDirect, ProQuest, and Google Scholar. We will include clinical practice guidelines, treatment protocols, systematic reviews, and clinical trials according to the three research questions to be answered related to nutrition therapy and interventions in ALS patients. This protocol will be developed in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P). To evaluate the methodological quality of the studies, AGREE II, Cochrane Risk of Bias (RoB 2.0), and ROBINS-I tools will be used. In addition, The Grading of Recommendations Assessment, Development and Evaluation (short GRADE) will be used to assess the quality of evidence and the strength of the recommendations. The findings will be summarized and presented descriptively according to the Cochrane Collaboration Handbook and the standard statistical meta-analysis techniques.

Ethics and dissemination: Ethical approval and human consent are not required because this is a protocol for systematic review and only secondary data will be used. Findings will be published in a peer-reviewed journal and presented at conferences. In case of any changes in this protocol,

amendments will be updated in PROSPERO and the modifications will be explained in the final report of this review.

PROSPERO registration number: CRD42021233088.

Keywords: amyotrophic lateral sclerosis, nutrition therapy, quality of health care

Strengths and limitations of this study:

- This protocol encompasses two systematic reviews.
- This protocol adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement guidelines.
- The methodological quality of the studies will be performed using the AGREE II statement.
- The methodological quality and risk of bias of clinical trials will be accomplished using the Cochrane Risk of Bias (RoB 2.0) and ROBINS-I tools for randomized and non-randomized studies, respectively.
- Meta-analysis may not be possible for certain outcomes due to a limited number of eligible studies.

INTRODUCTION

ALS is a multisystemic neurodegenerative disease characterized by progressive cell death of upper and lower motor neurons.[1, 2] Worldwide ALS prevalence varies from 1.57 cases per 100,000 to 9.62 per 100,000. Its incidence varies from 0.42 per 100,000 to 2.76 per 100,000 people/year. Both ALS prevalence and incidence are higher in developed regions.[3] Clinical signs of the disease have a low incidence before age 50 years, with a peak around age 85 years

followed by a marked decrease in incidence. However, the onset of this disease is rarely possible in early adulthood.[4] The severity of the disease points to a short median survival of 3 to 4 years after the initial diagnosis.[5-8]

Malnutrition is a frequent condition in patients with ALS, with prevalence ranging from 16 to 53%.[9] The Body Mass Index (BMI) is an important anthropometric parameter for diagnosing malnutrition among these patients. BMI reduction is related to faster disease progression and increased risk of mortality.[10] Marin et al.[11] demonstrated that 5% of body weight loss increases the risk of death by 30% in patients with ALS. Thus, nutritional care is essential for maintaining adequate nutritional status, which positively affects these patients' functional capacity, quality of life, and survival time.[12-14]

Several risk factors such as dysphagia, anorexia, gastrointestinal disorders, cognitive impairment, apathy, psychological disorders, and inadequate energy and nutrient intake contribute to malnutrition in patients with ALS. In addition, hypermetabolism may be present and can increase the risk of malnutrition or aggravate this condition, especially in the absence of nutritional care.[15, 16] Therefore, evidence-based nutritional interventions for ALS are of the utmost importance and must consider the different stages of the disease.[17]

Clinical Practice Guidelines (CPGs) have been developed to provide scientific evidence to support clinical decision-making of health professionals and establish standards of care for many conditions.[18, 19] CPGs focused on all aspects of nutritional therapy for ALS are still lacking. Existent guidelines on this matter only address some nutritional aspects, most of them related to gastrostomy and dysphagia. Many other aspects of nutritional therapy have not been covered, such as energy and nutrient requirements, modified consistency diet, micronutrients and bioactive compounds supplementation, and nutrition advice for comorbidities in ALS patients.

Considering this gap and aiming to provide broader guidance on nutrition therapy for ALS patients, it is essential to gather and synthesize recommendations on this subject, based on available scientific evidence of clinical protocols and guidelines. Also, based on the effectiveness of nutritional interventions verified through clinical trials. We believe that a synthesis of recommendations on nutrition therapy in ALS will help and guide the nutrition care process and benefit the patients.[20, 21]

Given the information above, this protocol will seek to answer the following questions: **RQ1** - What are the evidence-based nutritional recommendations to maintain or restore the nutritional status of patients with ALS? **RQ2** - What is the effect of a diet rich in energy and protein in people with ALS? **RQ3** - What are the effects of supplementing isolated micronutrients or bioactive compounds in people with ALS?

Therefore, this protocol aims to build an outline of upcoming systematic reviews and meta-analyses to present a synthesis of evidence-based recommendations to support adequate nutrition therapy and improve the nutritional status of patients with ALS.

METHODS AND ANALYSIS

Protocol Registration

This protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO) database on April 12, 2021 (CRD42021233088). This protocol is in line with international ethical parameters and because it is a study with secondary data, there is no need to seek approval from a research ethics committee. Also, it was developed in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P) statement guidelines.[22] The PRISMA-P checklist used to prepare this protocol has been

provided as an online supplemental file. To report the systematic review, the PRISMA statement with a 27-item checklist and descriptive flow diagram will be used.[23] This present protocol encompasses two systematic reviews and meta-analyses. The first one will be a review of protocols/guidelines aimed to answer the RQ1. The second one will be a review of clinical trials aimed to answer RQ2 and RQ3. The information regarding methods and analysis are described according to the research questions.

Selection Criteria

For RQ1, we will include CPGs, treatment protocols, and systematic reviews. For RQ2 and RQ3, we will only include clinical trials with control groups.

Participants

For all RQ's we will include studies comprised of adults (aged 18 and over) and seniors of both sexes with a clinical diagnosis of ALS as defined, probable, or possible.

Types of interventions

For RQ1, we will include studies involving nutrition therapy recommendations to maintain or restore the nutritional status of patients with ALS. For RQ2, we will include studies implementing a diet rich in energy and/or protein as an intervention. For RQ3, we will include studies supplementing single micronutrients or bioactive compounds as an intervention.

Outcomes measures

For RQ1, only the summary of the nutritional recommendations for recovery or maintenance of the nutritional status in ALS patients will be performed, with no outcomes to be measured. For the RQ2, the outcome will be the change of body mass index, percentage of weight loss, progression rate of total revised ALS Functional Rating Scale (ALSFRS-R), and mortality rate. For the RQ3, the outcome will be the antioxidant effect, ALSFRS-R progression rate, and mortality rate.

Inclusion Criteria

For RQ1, the inclusion criteria are evidence-based nutritional recommendations to maintain or restore the nutritional status of patients diagnosed with definite, probable, or possible ALS. For RQ2 and RQ3, the inclusion criteria are adults and elderly patients, of both sexes, diagnosed with definite, probable, or possible ALS.

Exclusion Criteria

For all RQ's we will exclude studies with other neurodegenerative diseases or without nutritional recommendations. No restrictions of time and language will be applied in our search.

Search strategy

A comprehensive electronic search will be performed in the following databases: PubMed, Excerpta Medica Database (Embase), Scopus, SciELO, Web of Science, LILACS, Cochrane Central Register of Controlled Trials (CENTRAL), ScienceDirect, ProQuest, and Google Scholar. The search strategy will include the following descriptors (MeSH): “Amyotrophic Lateral Sclerosis”, “Motor Neuron Disease”, “Nutrition”, “Nutritional Assessment”, “Nutrition

Therapy", "Diet", "Dietary Supplements", "Deglutition Disorders", "Guideline", and "Clinical Protocols". In addition, the EMTREE terms "Diet Therapy", "Dysphagia", and "Practice Guideline" will be included for the Embase database. A draft of our search strategy has been provided as an online supplemental file.

Searches of other resources

To ensure the comprehensiveness of this research, we will supplement searches by hand-searching in the reference lists of retrieved studies or relevant reviews. To identify unpublished studies and assess publication bias, we will also examine *ClinicalTrials.gov* and *ensaiosclinicos.gov.br* for registered clinical trials using interventions such as high-energy and/or high-protein diet and supplementation of micronutrients or bioactive compounds in people with ALS.

Study selection

For all identified studies, at least 2 authors (MDCV and LLL) will independently select and review titles and abstracts using the Rayyan QCRI® tool. Papers that meet the inclusion criteria will be ordered for a full review. Any disagreement will be resolved by discussion with a third reviewer (SHLV). A manual search will be performed if any relevant studies are found using the defined search strategies. All investigators will then review the full text of all eligible studies. The information on the phases of the selection process will be described through PRISMA flow diagram.[23]

Data extraction

The data extraction will be done in a standardized way, using Microsoft Excel by 2 independent authors (MDCV and LLL). Discrepancies between the data extraction will be resolved by consensus. The study characteristics will be collated according to the research questions. For RQ1, the following data will be extracted: general information about the guideline (title, responsible organization, year of publication, and funding); nutritional recommendations addressed; and the stratification of the level of evidence used. For RQ2 and RQ3, the following data will be extracted: general information (title, authors, journal, year, country); study characteristics (study design, study duration); sample characteristics (sample size, mean age, ALS subtype, ALSFRS-R); intervention (type of intervention, duration, diet characteristics, energy and/or protein amount); outcomes (changes in body mass index, percentage of weight loss, progression rate of functional status, mortality rate); and statistical results. If study reports are incomplete or missing data, corresponding authors will be contacted. If we do not receive clarification, the requested data will be excluded from our analysis and will be commented in the Discussion section.

Evaluation of methodological quality

Two independent authors (SHLV and MDCV) will evaluate the methodological quality of the studies using the AGREE II statement. This instrument assesses six domains: 1. Scope and purpose, 2. Stakeholder involvement, 3. Rigour of development, 4. Clarity of presentation, 5. Applicability, and 6. Editorial independence.[24] To assess the methodological quality and risk of bias of clinical trials, the Cochrane Risk of Bias (RoB 2.0) and ROBINS-I tools will be used for randomized and non-randomized studies, respectively.[25, 26]

Data synthesis

For the first systematic review (RQ1), the findings and main recommendations will be narratively summarized. For the second systematic review (RQ2 and RQ3), meta-analysis will be performed, if possible. If meta-analysis is not possible, we will conduct a systematic review with narrative analysis tabling the results.

Assessment of heterogeneity

To assess the heterogeneity, we plan to calculate the standard chi-square statistic, which is a quantitative measure of inconsistency between the studies. Next, the I^2 index will be calculated to quantify heterogeneity. The I^2 statistic describes the percentage of variation across studies due to heterogeneity rather than chance. No heterogeneity is observed when I^2 is 0%, and the variability can be explained by chance alone. A value of I^2 >50% indicates high heterogeneity.

Meta-analysis

If there is the possibility of meta-analysis, standard statistical techniques will be used. If substantial heterogeneity occurs, we will perform subgroup analysis and meta-regression to identify possible associated cofactors such as disease onset (bulbar or spinal), age at onset, disease duration, and clinical stages of ALS (early, middle, late, and end). In addition, the random effects model will be used in the synthesis of data from the included studies. Publication bias will be assessed using a funnel plot and its asymmetry will be verified by linear regression.

Subgroup analysis

For the RQ1 the analysis of subgroups is not applicable. If sufficient data are available for the RQ2 and RQ3, the subgroup analysis will consider disease onset (bulbar or spinal), age of onset, disease duration, and clinical stages of ALS (early, middle, late, and end). These stages are classified as follow: stage 1 for symptom onset or functional involvement of one Central System Nervous (CSN) region (**early**), stage 2 for diagnosis or functional involvement of two CSN regions (**middle**), stage 3 for functional involvement of three CSN regions (**late**), stage 4 for need for gastrostomy or non-invasive ventilation (**end**), and stage 5 for death.[27, 28]

Assessment of quality of evidence (GRADE)

Two independent authors (MDCV and LLL) will assess the quality of the evidence and the strength of the recommendations provided by the selected studies. For this purpose, we will use the Grading of Recommendations, Assessment, Development and Evaluation (GRADE)[29] for decision-making in health, which classifies the quality of evidence into four levels (high, moderate, low, and very low) and the strength of the evidence into two levels (strong or weak).

Patient and public involvement

No patients or the public will be directly engaged in this research, as it is conducted using secondary data.

DISCUSSION

This study aims to gather and synthesize recommendations for nutritional intervention and treatment based on available scientific evidence from clinical protocols and guidelines. Also, the effectiveness of interventions will be verified through clinical trials.

Weight loss, low BMI, and malnutrition are frequent in ALS patients. According to the guideline conducted by Burgos et al.,[30] the BMI reduction in ALS patients is associated with shortened survival and high risk of mortality.

A systematic review states that there is no cure or effective treatment for ALS to date. Multidisciplinary care is the basis for its treatment, including nutritional support as well as respiratory and symptom management during the disease. Furthermore, the review highlights that dietary intervention can help to improve nutrition status. For example, gastrostomy is indicated if oral intake is insufficient or is no longer safe.[31]

Dorst et al. found that high-energy supplementation effectively stabilizes the body weight of patients with ALS and no side effects were detected. The authors also observed a positive impact on the survival of the patients. Thus, the use of high-energy supplementation was suggested.[32] In a cohort study, Traynor et al.[33] demonstrated that ALS patients who received multidisciplinary care had a better prognosis than patients who received general care through a neurology clinic.

Scientific entities specialized in ALS recognize nutrition as integral part of care during the course of the disease and address some nutritional recommendations.[34, 35] Nutrition therapy seeks to prevent malnutrition, maintain adequate nutritional status, promote hemodynamic stability, reduce the rate of disease progression, and positively impact the quality of life and survival of ALS patients.[36] Thus, identifying consistent recommendations for nutrition intervention in ALS is of the utmost importance and will contribute to more assertive patient care.[37-40] Nevertheless, systematic reviews and guidelines about ALS nutritional therapy are scarce and some of them present gaps because they do not discuss specific aspects regarding nutritional treatment and management that should be implemented in this type of patient.

For example, the recommendations by Garcia et al.[41] describe the nutritional aspects of ALS and nutritional management with recommendations for high energy intake and those related to enteral and parenteral nutrition. However, it does not address percentages of macronutrients distribution, micronutrients requirements, or adjuvant nutritional supplements.

In a review paper about nutrition management in ALS, Greenwood et al.[39] prioritize the quantitative recommendation of protein but do not determine recommendations for lipids, carbohydrates, fibers, micronutrients, bioactive compounds, and nutritional supplements. The pieces of information we gathered show how these two systematic reviews proposed by our group are needed and can be helpful in assisting the nutrition care of ALS patients with robust recommendations based on scientific evidence.

In this sense, the development of updated systematic reviews with meta-analyses and synthesized recommendations on nutrition therapy of patients with ALS can reduce the nutritional risk and positively influence their quality of life and survival time. Furthermore, it will support the first Brazilian guideline of nutrition therapy in ALS, which will guide the clinical nutrition practice with greater safety and efficiency. Thus, we believe this protocol is relevant and it will benefit the scientific community, health care professionals, caregivers, and especially patients with ALS. In addition, the systematic reviews proposed can also help to highlight areas that require more research in the subject of nutrition therapy and ALS.

ETHICS AND DISSEMINATION

Ethical approval and human consent are not required because this is a protocol for systematic review and only secondary data will be used. Findings will be published in a peer-reviewed journal and presented at conferences. In case of any changes in this protocol, amendments will

be updated in PROSPERO and explanations of these modifications will be described in the final report of this review.

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CONTRIBUTORS

MDCV, LLL, and GP conceptualized and designed the protocol. The protocol manuscript was written by MDCV and LLL. It was critically reviewed by GP, GCBSM, KMDC, SHLV, and JBN. The search strategy was developed by MDCV, LLL, SHLV, GP, and GCBSM. MDCV, KMDC, and LLL will lead the study selection. MDCV, LLL, and KMDC will be responsible for data extraction. Statistical analysis will be performed by MDCV, SHLV, LLL, GCBSM, and GP. JBN will be the third party and will host consensus meetings at each stage in case of disagreement. All authors read, reviewed, and approved the final protocol.

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COMPETING INTERESTS

None declared.

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PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	X		OK*
Update	1b	If the protocol is for an update of a previous systematic review, identify as such		X	NA
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	X		26
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	X		OK*
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	X		277-284
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments		X	NA
Support					
Sources	5a	Indicate sources of financial or other support for the review	X		286-290
Sponsor	5b	Provide name for the review funder and/or sponsor	X		286-290
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol		X	NA
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	X		58-73
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	X		74-76
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	X		104-127

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	X		104-127
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	X		129-146
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	X		148-158
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	X		148-155
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	X		157-160; 168-171
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	X		161-168
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	X		161-168
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	X		173-179
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	X		181-185
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	X		187-201
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	X		203-206
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	X		182-185
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	X		200-201
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	X		208-213

* The title is included in the Step 1 of the submission process at BMJ Open's author dashboard. The title is in accordance with PRISMA-P recommendations.

Supplemental Material [Draft of Search Strategy]

Database	Research Question (QR)	Equations
PubMed	RQ1*	"amyotrophic lateral sclerosis" OR "motor neuron disease" AND "nutrition" AND "guideline"
PubMed	RQ2**	"amyotrophic lateral sclerosis" OR "motor neuron disease" AND "diet therapy" OR "diet, high fat" OR "diet, high protein"
PubMed	RQ3***	"amyotrophic lateral sclerosis" OR "motor neuron disease" AND "dietary supplements"
*RQ1 - What are the evidence-based nutritional recommendations to maintain or restore the nutritional status of patients with ALS? **RQ2 - What is the effect of a diet rich in energy and protein in people with ALS? ***RQ3 - What are the effects of supplementing isolated micronutrients or bioactive compounds in people with ALS?		

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Nutritional therapy in amyotrophic lateral sclerosis: Protocol for a systematic review and meta-analysis

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Nutritional therapy in amyotrophic lateral sclerosis: Protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction: Amyotrophic Lateral Sclerosis (ALS) is a complex neurodegenerative disease characterized by the degeneration of motor neurons. Nutritional interventions in ALS are essential and must be based on scientific evidence to provide quality of health care, improve the quality of life, and increase survival time. Therefore, this protocol of systematic reviews and meta-analyses aims to present a synthesis of evidence-based recommendations to support adequate nutrition therapy for patients with ALS.

Methods and analysis: The search will be performed using the following databases: PubMed, Excerpta Medica Database (Embase), Scopus, SciELO, Web of Science, LILACS, Cochrane Central Register of Controlled Trials (CENTRAL), ScienceDirect, ProQuest, and Google Scholar. We will include clinical practice guidelines, treatment protocols, systematic reviews, and clinical trials according to the three research questions to be answered related to nutrition therapy and interventions in ALS patients. This protocol will be developed in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P). To evaluate the methodological quality of the studies, AGREE II, Cochrane Risk of Bias (RoB 2.0), and ROBINS-I tools will be used. In addition, The Grading of Recommendations Assessment, Development and Evaluation (short GRADE) will be used to assess the quality of evidence and the strength of the recommendations. The findings will be summarized and presented descriptively according to the Cochrane Collaboration Handbook and the standard statistical meta-analysis techniques.

Ethics and dissemination: Ethical approval and human consent are not required because this is a protocol for systematic review and only secondary data will be used. Findings will be published in a peer-reviewed journal and presented at conferences. In case of any changes in this protocol,

amendments will be updated in PROSPERO and the modifications will be explained in the final report of this review.

PROSPERO registration number: CRD42021233088.

Keywords: amyotrophic lateral sclerosis, nutrition therapy, quality of health care

Strengths and limitations of this study:

- This protocol encompasses two systematic reviews.
- This protocol adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement guidelines.
- The methodological quality of the studies will be performed using the AGREE II statement.
- The methodological quality and risk of bias of clinical trials will be accomplished using the Cochrane Risk of Bias (RoB 2.0) and ROBINS-I tools for randomized and non-randomized studies, respectively.
- Meta-analysis may not be possible for certain outcomes due to a limited number of eligible studies.

INTRODUCTION

ALS is a multisystemic neurodegenerative disease characterized by progressive cell death of upper and lower motor neurons.[1, 2] Worldwide ALS prevalence varies from 1.57 cases per 100,000 to 9.62 per 100,000. Its incidence varies from 0.42 per 100,000 to 2.76 per 100,000 people/year. Both ALS prevalence and incidence are higher in developed regions.[3] Clinical signs of the disease have a low incidence before age 50 years, with a peak around age 85 years

followed by a marked decrease in incidence. However, the onset of this disease is rarely possible in early adulthood.[4] The severity of the disease points to a short median survival of 3 to 4 years after the initial diagnosis.[5-8]

Malnutrition is a frequent condition in patients with ALS, with prevalence ranging from 16 to 53%.[9] The Body Mass Index (BMI) is an important anthropometric parameter for diagnosing malnutrition among these patients. BMI reduction is related to faster disease progression and increased risk of mortality.[10] Marin et al.[11] demonstrated that 5% of body weight loss increases the risk of death by 30% in patients with ALS. Thus, nutritional care is essential for maintaining adequate nutritional status, which positively affects these patients' functional capacity, quality of life, and survival time.[12-14]

Several risk factors such as dysphagia, anorexia, gastrointestinal disorders, cognitive impairment, apathy, psychological disorders, and inadequate energy and nutrient intake contribute to malnutrition in patients with ALS. In addition, hypermetabolism may be present and can increase the risk of malnutrition or aggravate this condition, especially in the absence of nutritional care.[15, 16] Therefore, evidence-based nutritional interventions for ALS are of the utmost importance and must consider the different stages of the disease.[17]

Clinical Practice Guidelines (CPGs) have been developed to provide scientific evidence to support clinical decision-making of health professionals and establish standards of care for many conditions.[18, 19] CPGs focused on all aspects of nutritional therapy for ALS are still lacking. Existent guidelines on this matter only address some nutritional aspects, most of them related to gastrostomy and dysphagia. Many other aspects of nutritional therapy have not been covered, such as energy and nutrient requirements, modified consistency diet, micronutrients and bioactive compounds supplementation, and nutrition advice for comorbidities in ALS patients.

Considering this gap and aiming to provide broader guidance on nutrition therapy for ALS patients, it is essential to gather and synthesize recommendations on this subject, based on available scientific evidence of clinical protocols and guidelines. Also, based on the effectiveness of nutritional interventions verified through clinical trials. We believe that a synthesis of recommendations on nutrition therapy in ALS will help and guide the nutrition care process and benefit the patients.[20, 21]

Given the information above, this protocol will seek to answer the following questions: **RQ1** - What are the evidence-based nutritional recommendations to maintain or restore the nutritional status of patients with ALS? **RQ2** - What is the effect of a diet rich in energy and protein in people with ALS? **RQ3** - What are the effects of supplementing isolated micronutrients or bioactive compounds in people with ALS?

Therefore, this protocol aims to build an outline of upcoming systematic reviews and meta-analyses to present a synthesis of evidence-based recommendations to support adequate nutrition therapy and improve the nutritional status of patients with ALS.

METHODS AND ANALYSIS

Protocol Registration

This protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO) database on April 12, 2021 (CRD42021233088). This protocol is in line with international ethical parameters and because it is a study with secondary data, there is no need to seek approval from a research ethics committee. Also, it was developed in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P) statement guidelines.[22] The PRISMA-P checklist used to prepare this protocol has been

provided as an online supplemental file. To report the systematic review, the PRISMA statement with a 27-item checklist and descriptive flow diagram will be used.[23] This present protocol encompasses two systematic reviews and meta-analyses. The first one will be a review of protocols/guidelines aimed to answer the RQ1. The second one will be a review of clinical trials aimed to answer RQ2 and RQ3. The information regarding methods and analysis are described according to the research questions.

Selection Criteria

For RQ1, we will include CPGs, treatment protocols, and systematic reviews. For RQ2 and RQ3, we will only include clinical trials with control groups.

Participants

For all RQ's we will include studies comprised of adults (aged 18 and over) and seniors of both sexes with a clinical diagnosis of ALS as definite, probable, or possible, according to the revised El Escorial criteria.

Types of interventions

For RQ1, we will include studies involving nutrition therapy recommendations to maintain or restore the nutritional status of patients with ALS. For RQ2, we will include studies implementing a diet rich in energy and/or protein as an intervention. For RQ3, we will include studies supplementing single micronutrients or bioactive compounds as an intervention.

Outcomes measures

For RQ1, only the summary of the nutritional recommendations for recovery or maintenance of the nutritional status in ALS patients will be performed, with no outcomes to be measured. For the RQ2, the outcome will be the change of body mass index, percentage of weight loss, progression rate of total revised ALS Functional Rating Scale (ALSFRS-R), and mortality rate. For the RQ3, the outcome will be the antioxidant effect, ALSFRS-R progression rate, and mortality rate.

Inclusion Criteria

For RQ1, the inclusion criteria are evidence-based nutritional recommendations to maintain or restore the nutritional status of patients diagnosed with definite, probable, or possible ALS. For RQ2 and RQ3, the inclusion criteria are adults and elderly patients, of both sexes, diagnosed with definite, probable, or possible ALS.

Exclusion Criteria

For all RQ's we will exclude studies with other neurodegenerative diseases or without nutritional recommendations. No restrictions of time and language will be applied in our search.

Search strategy

A comprehensive electronic search will be performed in the following databases: PubMed, Excerpta Medica Database (Embase), Scopus, SciELO, Web of Science, LILACS, Cochrane Central Register of Controlled Trials (CENTRAL), ScienceDirect, ProQuest, and Google Scholar. The search strategy will include the following descriptors (MeSH): “Amyotrophic Lateral Sclerosis”, “Motor Neuron Disease”, “Nutrition”, “Nutritional Assessment”, “Nutrition

Therapy", "Diet", "Dietary Supplements", "Deglutition Disorders", "Guideline", and "Clinical Protocols". In addition, the EMTREE terms "Diet Therapy", "Dysphagia", and "Practice Guideline" will be included for the Embase database. A draft of our search strategy has been provided as an online supplemental file.

Searches of other resources

To ensure the comprehensiveness of this research, we will supplement searches by hand-searching in the reference lists of retrieved studies or relevant reviews. To identify unpublished studies and assess publication bias, we will also examine *ClinicalTrials.gov* and *ensaiosclinicos.gov.br* for registered clinical trials using interventions such as high-energy and/or high-protein diet and supplementation of micronutrients or bioactive compounds in people with ALS.

Study selection

For all identified studies, at least 2 authors (MDCV and LLL) will independently select and review titles and abstracts using the Rayyan QCRI® tool. Papers that meet the inclusion criteria will be ordered for a full review. Any disagreement will be resolved by discussion with a third reviewer (SHLV). A manual search will be performed if any relevant studies are found using the defined search strategies. All investigators will then review the full text of all eligible studies. The information on the phases of the selection process will be described through PRISMA flow diagram.[23]

Data extraction

The data extraction will be done in a standardized way, using Microsoft Excel by 2 independent authors (MDCV and LLL). Discrepancies between the data extraction will be resolved by consensus. The study characteristics will be collated according to the research questions. For RQ1, the following data will be extracted: general information about the guideline (title, responsible organization, year of publication, and funding); nutritional recommendations addressed; and the stratification of the level of evidence used. For RQ2 and RQ3, the following data will be extracted: general information (title, authors, journal, year, country); study characteristics (study design, study duration); sample characteristics (sample size, mean age, ALS subtype, ALSFRS-R); intervention (type of intervention, duration, diet characteristics, energy and/or protein amount); outcomes (changes in body mass index, percentage of weight loss, progression rate of functional status, mortality rate); and statistical results. If study reports are incomplete or missing data, corresponding authors will be contacted. If we do not receive clarification, the requested data will be excluded from our analysis and will be commented in the Discussion section.

Evaluation of methodological quality

Two independent authors (SHLV and MDCV) will evaluate the methodological quality of the studies using the AGREE II statement. This instrument assesses six domains: 1. Scope and purpose, 2. Stakeholder involvement, 3. Rigour of development, 4. Clarity of presentation, 5. Applicability, and 6. Editorial independence.[24] To assess the methodological quality and risk of bias of clinical trials, the Cochrane Risk of Bias (RoB 2.0) and ROBINS-I tools will be used for randomized and non-randomized studies, respectively.[25, 26]

Data synthesis

For the first systematic review (RQ1), the findings and main recommendations will be narratively summarized. For the second systematic review (RQ2 and RQ3), meta-analysis will be performed, if possible. If meta-analysis is not possible, we will conduct a systematic review with narrative analysis tabling the results.

Assessment of heterogeneity

To assess the heterogeneity, we plan to calculate the standard chi-square statistic, which is a quantitative measure of inconsistency between the studies. Next, the I^2 index will be calculated to quantify heterogeneity. The I^2 statistic describes the percentage of variation across studies due to heterogeneity rather than chance. No heterogeneity is observed when I^2 is 0%, and the variability can be explained by chance alone. A value of I^2 >50% indicates high heterogeneity.

Meta-analysis

If there is the possibility of meta-analysis, standard statistical techniques will be used. If substantial heterogeneity occurs, we will perform subgroup analysis and meta-regression to identify possible associated cofactors such as disease onset (bulbar or spinal), age at onset, disease duration, and clinical stages of ALS (early, middle, late, and end). In addition, the random effects model will be used in the synthesis of data from the included studies. Publication bias will be assessed using a funnel plot and its asymmetry will be verified by linear regression.

Subgroup analysis

For the RQ1 the analysis of subgroups is not applicable. If sufficient data are available for the RQ2 and RQ3, the subgroup analysis will consider disease onset (bulbar or spinal), age of onset, disease duration, and clinical stages of ALS (early, middle, late, and end). These stages are classified as follow: stage 1 for symptom onset or functional involvement of one Central Nervous System (CNS) region (**early**), stage 2 for diagnosis or functional involvement of two CNS regions (**middle**), stage 3 for functional involvement of three CNS regions (**late**), stage 4 for need for gastrostomy or non-invasive ventilation (**end**), and stage 5 for death.[27, 28]

Assessment of quality of evidence (GRADE)

Two independent authors (MDCV and LLL) will assess the quality of the evidence and the strength of the recommendations provided by the selected studies. For this purpose, we will use the Grading of Recommendations, Assessment, Development and Evaluation (GRADE)[29] for decision-making in health, which classifies the quality of evidence into four levels (high, moderate, low, and very low) and the strength of the evidence into two levels (strong or weak).

Patient and public involvement

No patients or the public will be directly engaged in this research, as it is conducted using secondary data.

DISCUSSION

This study aims to gather and synthesize recommendations for nutritional intervention and treatment based on available scientific evidence from clinical protocols and guidelines. Also, the effectiveness of interventions will be verified through clinical trials.

Weight loss, low BMI, and malnutrition are frequent in ALS patients. According to the guideline conducted by Burgos et al.,[30] the BMI reduction in ALS patients is associated with shortened survival and high risk of mortality.

A systematic review states that there is no cure or effective treatment for ALS to date. Multidisciplinary care is the basis for its treatment, including nutritional support as well as respiratory and symptom management during the disease. Furthermore, the review highlights that dietary intervention can help to improve nutrition status. For example, gastrostomy is indicated if oral intake is insufficient or is no longer safe.[31]

Dorst et al. found that high-energy supplementation effectively stabilizes the body weight of patients with ALS and no side effects were detected. The authors also observed a positive impact on the survival of the patients. Thus, the use of high-energy supplementation was suggested.[32] In a cohort study, Traynor et al.[33] demonstrated that ALS patients who received multidisciplinary care had a better prognosis than patients who received general care through a neurology clinic.

Scientific entities specialized in ALS recognize nutrition as integral part of care during the course of the disease and address some nutritional recommendations.[34, 35] Nutrition therapy seeks to prevent malnutrition, maintain adequate nutritional status, promote hemodynamic stability, reduce the rate of disease progression, and positively impact the quality of life and survival of ALS patients.[36] Thus, identifying consistent recommendations for nutrition intervention in ALS is of the utmost importance and will contribute to more assertive patient care.[37-40] Nevertheless, systematic reviews and guidelines about ALS nutritional therapy are scarce and some of them present gaps because they do not discuss specific aspects regarding nutritional treatment and management that should be implemented in this type of patient.

For example, the recommendations by Garcia et al.[41] describe the nutritional aspects of ALS and nutritional management with recommendations for high energy intake and those related to enteral and parenteral nutrition. However, it does not address percentages of macronutrients distribution, micronutrients requirements, or adjuvant nutritional supplements.

In a review paper about nutrition management in ALS, Greenwood et al.[39] prioritize the quantitative recommendation of protein but do not determine recommendations for lipids, carbohydrates, fibers, micronutrients, bioactive compounds, and nutritional supplements. The pieces of information we gathered show how these two systematic reviews proposed by our group are needed and can be helpful in assisting the nutrition care of ALS patients with robust recommendations based on scientific evidence.

In this sense, the development of updated systematic reviews with meta-analyses and synthesized recommendations on nutrition therapy of patients with ALS can reduce the nutritional risk and positively influence their quality of life and survival time. Furthermore, it will support the first Brazilian guideline of nutrition therapy in ALS, which will guide the clinical nutrition practice with greater safety and efficiency. Thus, we believe this protocol is relevant and it will benefit the scientific community, health care professionals, caregivers, and especially patients with ALS. In addition, the systematic reviews proposed can also help to highlight areas that require more research in the subject of nutrition therapy and ALS.

ETHICS AND DISSEMINATION

Ethical approval and human consent are not required because this is a protocol for systematic review and only secondary data will be used. Findings will be published in a peer-reviewed journal and presented at conferences. In case of any changes in this protocol, amendments will

be updated in PROSPERO and explanations of these modifications will be described in the final report of this review.

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CONTRIBUTORS

MDCV, LLL, and GP conceptualized and designed the protocol. The protocol manuscript was written by MDCV and LLL. It was critically reviewed by GP, GCBSM, KMDC, SHLV, and JBN. The search strategy was developed by MDCV, LLL, SHLV, GP, and GCBSM. MDCV, KMDC, and LLL will lead the study selection. MDCV, LLL, and KMDC will be responsible for data extraction. Statistical analysis will be performed by MDCV, SHLV, LLL, GCBSM, and GP. JBN will be the third party and will host consensus meetings at each stage in case of disagreement. All authors read, reviewed, and approved the final protocol.

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COMPETING INTERESTS

None declared.

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41. Del Olmo García MªD, Virgili Casas N, Cantón Blanco A, et al. Manejo nutricional de la esclerosis lateral amiotrófica: resumen de recomendaciones [Nutritional management of amyotrophic lateral sclerosis: summary of recommendations]. *Nutr Hosp* 2018;35(5):1243-1251.

Supplemental Material [Draft of Search Strategy]

Database	Research Question (QR)	Equations
PubMed	RQ1*	"amyotrophic lateral sclerosis" OR "motor neuron disease" AND "nutrition" AND "guideline"
PubMed	RQ2**	"amyotrophic lateral sclerosis" OR "motor neuron disease" AND "diet therapy" OR "diet, high fat" OR "diet, high protein"
PubMed	RQ3***	"amyotrophic lateral sclerosis" OR "motor neuron disease" AND "dietary supplements"
*RQ1 - What are the evidence-based nutritional recommendations to maintain or restore the nutritional status of patients with ALS? **RQ2 - What is the effect of a diet rich in energy and protein in people with ALS? ***RQ3 - What are the effects of supplementing isolated micronutrients or bioactive compounds in people with ALS?		

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	X		OK*
Update	1b	If the protocol is for an update of a previous systematic review, identify as such		X	NA
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	X		26
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	X		OK*
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	X		277-284
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments		X	NA
Support					
Sources	5a	Indicate sources of financial or other support for the review	X		286-290
Sponsor	5b	Provide name for the review funder and/or sponsor	X		286-290
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol		X	NA
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	X		58-73
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	X		74-76
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	X		104-127

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	X		104-127
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	X		129-146
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	X		148-158
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	X		148-155
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	X		157-160; 168-171
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	X		161-168
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	X		161-168
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	X		173-179
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	X		181-185
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	X		187-201
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	X		203-206
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	X		182-185
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	X		200-201
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	X		208-213

* The title is included in the Step 1 of the submission process at BMJ Open's author dashboard. The title is in accordance with PRISMA-P recommendations.