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Outcomes of Oral Protein Supplementation in Hospitalised Older Adults: A Systematic Review protocol of randomised controlled trials

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ABSTRACT

Introduction

The effects of acute illnesses, such as infection or trauma, may exacerbate sarcopenia through reduced oral intake of food, inflammation, and immobility. Without correction, this acute sarcopenia could contribute to increased frailty in a cycle of further illnesses and hospital admissions. Nutritional support may be a key factor in addressing this problem, however, clinicians do not currently offer routine protein supplementation to in-patients with frailty or at risk of sarcopenia.

Objective: To evaluate the effectiveness of oral protein supplementation versus usual care on clinical and resource use outcomes in hospitalised older adults. Also, to determine whether intervention and patient factors can influence the effectiveness of oral protein supplementation.

Inclusion criteria: Randomised Controlled Trials of hospitalised older adults (aged ≥65 years), on oral protein supplementation with usual care as comparator and one or more outcomes of interest (mortality, disability, physical performance, muscle strength, institutionalisation, in-patient complications, length of hospital stay and non-elective readmission). **Exclusion criteria:** are dietary counselling and parenteral or enteral tube feeding only, patients solely recovering from cancer treatment or with a new cancer diagnosis and patients in critical care units and terminally ill-patients.

Method

Electronic searches will be conducted in the following databases for relevant studies, MEDLINE, EMBASE, and Cumulative Index to Nursing & Allied Health from inception to March 2021 and search will be limited to English language. Two independent reviewers will screen the abstracts and titles, then full text papers, to apply the eligibility criteria. Any disagreements about eligibility will be discussed and resolved with a third reviewer. Critical appraisal, data extraction and data synthesis will be conducted using the Joanna Briggs Institute (JBI) SUMARI Software 2020.

Key words
Nutrition; acute illness; mortality; disability; resource use; elderly

INTRODUCTION

Many older adults admitted to hospital have frailty [1-3], which typically includes sarcopenia – reduced skeletal muscle strength and mass [4]. The effects of acute illnesses, such as infection or trauma may exacerbate sarcopenia through reduced oral intake of food, inflammation, and immobility [5]. Without correction, this acute sarcopenia [6] could contribute to increased frailty in a cycle of further illnesses and admissions.

Nutritional support is one of the many responses to address this problem[7-9]. Nurses and dieticians routinely screen for malnutrition and advise the best diets possible; nurses provide oral care and encourage patients to eat, sometimes oral nutritional supplements (ONS) are offered, and tube feeding is advised in some severe cases.

Much focus in malnutrition has hitherto been upon inadequate intake of calories, or of the diet in general [10]. Recognition of the role of sarcopenia in adverse outcomes and the importance of adequate ingestion of protein in the maintenance of muscle mass raises the possibility that specific protein supplementation may improve outcomes in this situation. However, clinicians do not currently offer routine protein supplementation to in-patients with frailty or at risk of sarcopenia.

Objectives

The aims of this review are:

- to determine the extent and strength of the published Randomised Controlled Trial evidence about the effect of oral protein supplementation (OPS) compared to usual care in older adults admitted acutely to hospital upon clinical outcomes (mortality, disability, physical performance, in-patient complications, muscle strength, nutritional status, institutionalisation), and

resource use (length of hospital stay and non-elective readmission rate) outcomes
- to determine intervention factors that influence the effectiveness of oral protein supplementation
- to determine patient factors that influence the effectiveness of oral protein supplementation

METHOD

Study registration

This systematic review protocol was registered on the International Prospective Register of Ongoing Systematic Reviews (PROSPERO) – CRD42021227777 and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis Protocol PRISMA-P [11].

Eligibility criteria

Inclusion criteria:

- Study – Randomised Controlled Trials (RCTs), including cluster and individually randomised trials
- Population – Older adults (aged ≥65 years)
- Population – Acute or rehabilitation hospital in-patient
- Intervention - oral dietary protein supplementation
- Control – usual care
- Outcomes including one or more of the outcomes of interest (mortality, disability, physical performance, muscle strength, nutritional status, institutionalisation, in-patient complications, length of hospital stay, and non-elective readmission)

Exclusion criteria:

- Intervention - dietary counselling only
- Intervention - parenteral or enteral tube feeding only
- Participants – patients solely recovering from cancer treatment or with a new cancer diagnosis
- Participants – patients in critical care units
- Participants - terminally ill patients
- Studies not published in English language

Information sources

Electronic searches will be conducted in the following databases for relevant studies, MEDLINE, EMBASE, and Cumulative Index to Nursing & Allied Health (CINAHL) from inception to December 2020.

Search strategy

Search strategies that will be used for the electronic database searches will include the search terms: older adults OR hospitalised OR acute illness AND oral protein supplementation. The reference lists of review articles identified in the electronic searches, and articles selected after identification by the electronic searches will be searched manually for relevant publications. Full search terms that will be used are (Elderly OR Geriatric* OR (older ADJ (people OR adult* OR person* OR female* OR women OR men OR male*))).ti,ab OR exp AGED/ AND (Hospitalis* OR Hospitaliz* OR ((Inpatient OR hospital OR medical OR healthcare OR "health care" OR acute*) ADJ1 (setting* OR admitted OR admission* OR centre* OR center* OR ward* OR unit* OR stay))).ti,ab OR HOSPITALIZATION/ OR INPATIENTS/ AND (acute* ADJ2 (ill OR illness* OR sick* OR unwell)).ti,ab OR "ACUTE DISEASE"/AND *"DIETARY PROTEINS"/ OR ((oral OR food* OR drink* OR sip OR supplement*) ADJ2 (protein* OR whey OR soy OR casein OR nutrition*)).ti,ab

Study records: data management

Joanna Briggs Institute (JBI) SUMARI Software 2020 will be used to handle the data, resolve duplications, record the reasons for exclusion, store the full texts in line with PRISMA guidelines, and for the synthesis of data.

Study records: selection process

Two independent reviewers will screen the abstracts and titles, then full text papers, to apply the eligibility criteria. Any disagreements about eligibility will be discussed and resolved with a third reviewer.

Study records: data collection process

Two reviewers will independently complete a pre-piloted Microsoft Excel 2019 data extraction spreadsheet. Disagreements about data extraction will be discussed and resolved with a third reviewer.

Data items

Study:

- First author
- Year of publication
- Country or countries
- Type of hospital (Acute or in-patient rehabilitation)
- RCT type (if stratified => variables if cluster => type)
- Eligibility criteria
- Total sample size
- Dropouts
- Description of main results

Patient characteristics:

- Age of participants (Range, Mean & Standard Deviation (SD)/Median & Interquartile Ratio (IQR)
- Participant's sex – Number (n)/Percentage (%)
- Body Mass Index (BMI) of participants – mean & SD & *P*-value
- Principal condition on admission – n (%)
- Comorbidities – n (%)

Intervention:

- Intervention group sample size - mean & SD / median & IQR/ proportion & %)
- Control group sample size - mean & SD / median & IQR/ proportion & %)
- Intervention type, dose, frequency, duration
- Co-additional interventions
- Compliance with interventions
- Adverse events of intervention

Outcomes measured:

- Nutritional status
- Sarcopenia (sarcopenia measure will be accepted if muscle strength, muscle mass, physical performance, or handgrip strength) is measured
- In-patient complications

- Length of hospital stay
- Readmissions (non-elective)
- Disability
- Residence of participants (own home, institution)
- Discharge destination/outcome (own home, institution or died during hospitalisation)
- Institutionalisation
- Death

Quality assessment:

- Study quality score (The GRADE profiler software (GRADEPRO) will be used to create "summary of finding" tables with outcome specific information concerning the overall quality of evidence)
- Study quality score explanation

Outcomes and prioritisation

Primary outcomes

- Mortality
- Disability
- Physical performance
- In-patient complications
- Muscle strength
- Nutritional status
- Institutionalisation
- Length of hospital stay
- Readmission (non-elective)

Risk of bias in individual studies

The Cochrane Collaboration's Risk of Bias tool for Randomised Controlled Trials will be used to assess the risk of bias in the included studies [12]. The following domains will be assessed: allocation concealment, blinding, selective reporting, incomplete outcome data, random sequence generation, and other bias. One of the most important issues in non-drug trials is the difference between the treatment and the control conditions. For

example, here the control groups will still be having some nutrition and so it is important to define both the treatment and control conditions to be able to determine the difference between them.

Data analysis

If the conditions for meta-analysis are met (where three or more studies with similar interventions/comparators, have measured the same outcome – mean and standard deviation), we will conduct a meta-analysis. We will pool the results using a random-effects meta-analysis using the JBI SUMARI Software 2020, with standardised mean differences for continuous outcomes and risk factors for binary outcomes and calculate 95% confidence intervals and two-sided *P* values for each outcome.

However, if quantitative synthesis is not appropriate for the analysis, we will conduct synthesis without meta-analysis (SWiM).

First will be a tabular analysis stage, in which a table will be produced including:

- the effect sizes for each trial and outcome are calculated ((treatment group mean- control group mean) / standard deviation) and classified using Cohen's classification in which no effect = <0.2, small = 0.2-0.49, medium = 0.5-0.8, and large = > 0.8.
- the quality grade of the study
- the size of the study

We will answer our primary research question by summarising the evidence for each outcome in a narrative synthesis using the following classification:

- No evidence (no studies have examined this outcome)
- Inadequate evidence (poor quality or small studies)
- Evidence of small effect (one or more studies of adequate quality and size showing a small effect)
- Evidence of medium effect (one or more studies of adequate quality and size showing a medium effect)
- Evidence of large effect (one or more studies of adequate quality and size showing a large effect)
- Inconsistent evidence (differing effect sizes between two or more studies of adequate size and quality)

Our interpretations will be guided by the principle that the most robust evidence will come from the better-quality studies, and that the findings of larger studies are more robust than smaller ones with similar design quality. For example, in our narrative synthesis we would favour the neutral findings of a large well conducted study over a poorly conducted small study showing a large effect size.

The limitations of this form of synthesis compared to a meta-analysis is that the result is qualitative (e.g., some evidence of a moderate treatment effect") rather than numerical (e.g., "Odds ratio 0.79, 95% confidence intervals 0.35 – 1.09").

Our secondary analyses will be:

- Patient factors influencing the oral protein supplementation upon outcomes in hospitalised older adults
- Intervention factors influencing oral protein supplementation upon outcomes in hospitalised older adults

There are no pre-planned sensitivity analyses.

Meta-bias

Our narrative synthesis will indicate where evidence is absent, allowing us to distinguish between "absence of evidence of effectiveness" from "evidence of absence of effectiveness". It will also allow us to report a synthesis of findings that is not swayed in favour of the results of weak or small studies.

Confidence in cumulative evidence

Our narrative synthesis will depend upon the robustness of the evidence under review by assessing the quality of the included studies, allowing us to indicate the confidence of our conclusions. The overall strength of the evidence will be analysed for each outcome using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool. This system represents a method that evaluates the quality of evidence in systematic reviews explicitly, comprehensively, transparently, and pragmatically [13]. The GRADE system evaluates the following dimensions regarding the quality of evidence: study limitations/risk of bias, inconsistency, indirect effects, inaccuracy, publication bias, and factors that may increase the quality of evidence. GRADE classifies the quality of

evidence into four different levels: high, moderate, low, and very low [13]. The GRADE profiler software (GRADEPRO) will be used to create "summary of finding" tables with outcome specific information concerning the overall quality of evidence and the magnitude of effects of the interventions investigated by the examined body of evidence, a similar method has been used elsewhere [14].

Ethical Approval

Ethical approval is not required for this systematic review.

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