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REVIEW ARTICLE

Major relevances of nutrological therapy and gut microbiota in neurodegenerative diseases: a systematic review

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Abstract

Introduction: Critical patients, both due to brain injury and neurodegenerative diseases, have an increased risk of developing nutritional malnutrition due to complex problems and deleterious effects of diseases on protein and energy metabolism, resulting in metabolic dysregulation, hypercatabolic state and depletion of energy reserves energy. **Objective:** It was to carry out a systematic review to externalize and discuss the main findings on the effects of enteral nutritional therapy, as well as on the action of the gut microbiota in patients with brain injuries or neurodegenerative diseases. **Methods:** The PRISMA Platform systematic review rules were followed. The search was carried out from March to May 2025 in the Web of Science, Scopus, Embase, PubMed, Science Direct, Scielo, and Google Scholar databases. The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed according to the Cochrane instrument. **Results and Conclusion:** A total of 108 articles were found, and 20 articles were evaluated in full, and 08 were included and developed in the present systematic review study. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 30 studies with a high risk of bias and 24 studies that did not meet GRADE and AMSTAR-2. Most studies showed homogeneity in their results, with X^2=88.9%>50%. Enteral nutrition supplemented with probiotics effectively decreases the risk of mortality, gastrointestinal complications, and infection, and shortens the length of stay in the intensive care unit, therefore, it should be widely adopted for the management of these patients. Nasal inspiratory pressure during a sniff at baseline is an early indicator of disease progression and therefore the need for enteral nutrition in amyotrophic lateral sclerosis. Furthermore, problems with tolerance, diarrhea, and abdominal distension decreased between the 3 and 6-month visits in patients who received home enteral nutrition.

Keywords: Nutrological therapy. Gut microbiota. Brain injuries. Neurodegenerative diseases.

Introduction

In the context of enteral therapy in patients with brain injuries or neurodegenerative diseases, critically ill patients have an increased risk of developing nutritional malnutrition due to complex problems and deleterious effects of the diseases on protein and energy metabolism, resulting in metabolic dysregulation, hypercatabolic state, and depletion of energy reserves **[1-4]**.

The provision of adequate and timely nutritional support for critically ill patients is therefore considered crucial **[5,6]**, given that protein deficiency and energy depletion in severely ill individuals have been associated with health problems, resulting in infections and increased mortality, as well as increased length of stay in the intensive care unit (ICU) and increased costs **[5,7-12]**.

For example, the incidence of malnutrition in stroke patients ranges from 6.1% to 62.0% depending on the method and timing of nutrition assessment **[13,14]**, while dysphagia was evident in approximately 50% of patients in the initial period **[15-17]**. Nutritional status is closely related to long-term clinical evolution among stroke patients and has an increased risk of post-stroke infection, recurrent stroke, and mortality in cases of malnutrition **[14,18]**.

In this sense, enteral nutritional therapy via the gastrointestinal tract is considered the first choice of nutritional support and a marker of quality of care for critically ill patients **[1,2]** as it is associated with protecting intestinal mucosal integrity, reducing infection rates, morbidity, and mortality. However, providing adequate nutritional support to critically ill patients remain a challenge due to the impact of the underlying diagnosis and concomitant treatments on nutrition **[2]**.

In this context, fortifying enteral formulas with prebiotics can enhance the adequacy of nutritional therapy by enabling targeted modifications in the composition and/or function of the gastrointestinal microbiota, thereby promoting host well-being **[1,19,20]**. Prebiotic fructo-oligosaccharides selectively stimulate the proliferation of bifidobacteria and potentially lactobacilli and provide a substrate for fermentation and short-chain fatty acid (SCFA) production **[21,22]**.

Although the effect of fructo-oligosaccharides on the colonic microbiota has been widely discussed in healthy populations, few clinical studies have investigated their use in enteral formulas, indicating the potential benefit of fructo-oligosaccharide content in stabilizing intestinal barrier homeostasis and reducing infection rates **[1,21]**. As a corollary to this, some clinical studies have explored the effect of enteral nutrition with probiotics on the clinical evolution of patients with brain lesions or neurodegenerative diseases, and have observed that early enteral nutrition with probiotics can improve intestinal homeostasis in these patients, thus improving other clinical outcomes **[1,21,22]**.

Therefore, the present study aimed to conduct a systematic review to present and discuss the main findings on the effects of nutritional therapy, as well as the action of the gut microbiota in patients with brain lesions or neurodegenerative diseases.

Methods

Study Design

This study followed an international model for systematic reviews, adhering to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Available at: http://www.prisma-statement.org/?AspxAutoDetectCookieSupport=1. Accessed on: 04/18/2025. The methodological quality standards of AMSTAR-2 (Assessing the methodological quality of systematic reviews) were also followed. Available at: https://amstar.ca/. Accessed on: 04/18/2025.

Data Sources and Research Strategy

The literature search process was conducted from March to May 2025 and developed based on Web of Science, Scopus, Embase, PubMed, Lilacs, Ebsco, Scielo, and Google Scholar, covering scientific articles from various periods to the present. The following descriptors (DeCS/MeSH Terms) were used: *"Nutrological therapy. Gut microbiota. Brain injuries. Neurodegenerative diseases"*, and using the Boolean operator "and" between MeSH terms and "or" between historical findings.

Study Quality and Risk of Bias

Quality was classified as high, moderate, low, or very low regarding the risk of bias, clarity of comparisons, precision, and consistency of analyses. The most evident highlight was for systematic review articles or meta-analyses of randomized clinical trials, followed by randomized clinical trials. Low-quality evidence was attributed to case reports, editorials, and brief communications, according to the GRADE instrument. The risk of bias was analyzed according to the Cochrane instrument by means of the Funnel Plot analysis (Sample size versus Effect size), using Cohen's d test.

Results and Discussion

Summary of Findings

A total of 108 articles were submitted to eligibility analysis, with 8 final studies selected to compose the results of this systematic review. The selected studies presented medium to high quality (Figure 1), considering the level of scientific evidence of studies such as meta-analyses, consensus studies, randomized clinical trials, prospective and observational studies. Biases did not compromise the scientific basis of the studies. According to the GRADE instrument, most studies showed homogeneity in their results, with X^2=88.9%>50%. Considering the Cochrane tool for risk of bias, the overall evaluation resulted in 30 studies with a high risk of bias and 24 studies that did not meet the GRADE and AMSTAR-2 criteria.

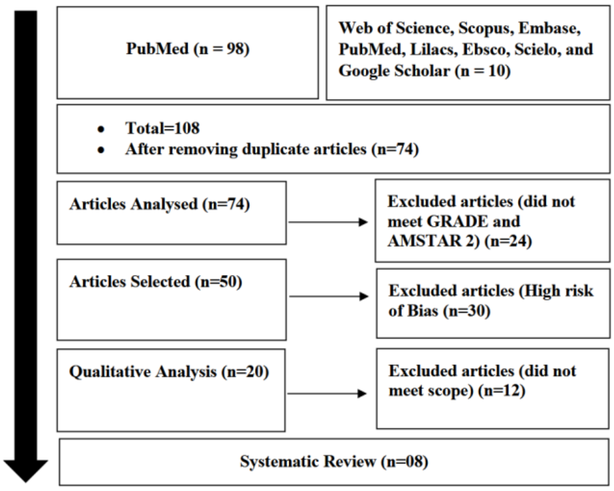

Figure 1. Selection of articles. Source: Own authorship.

Figure 2 presents the results of the risk of bias of the studies using the Funnel Plot, showing the calculation of the Effect Size (Magnitude of the difference) using Cohen's d test. Precision (sample size) was determined indirectly by the inverse of the standard error (1/Standard Error). This graph showed a symmetrical behavior, not suggesting a significant risk of bias, both among studies with small sample sizes (lower precision) shown at the bottom of the graph and studies with large sample sizes shown at the top.

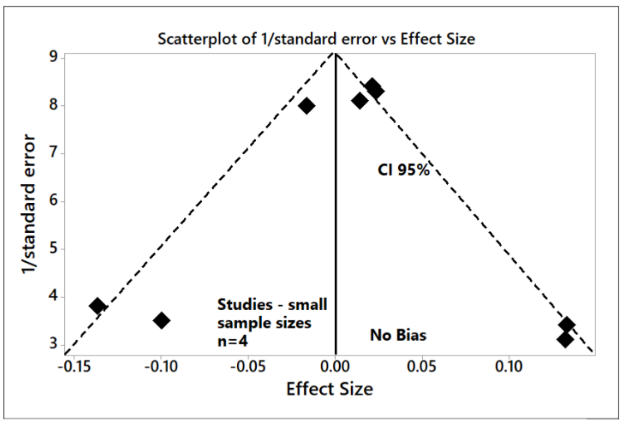

Figure 2. The symmetrical funnel plot does not suggest a risk of bias among the smasample size studies shown at the bottom of the graph (n=4). Studies with high confidence and high recommendation are shown above the graph (n=4). Source: Own authorship.

Main Results - Nutritional Therapy, Gut Microbiota and Neurodegenerative Diseases

According to the literature findings that were selected in this study, it was shown that the metabolites of the gut microbiota can be important for the health of the host, but few studies have investigated the correlation between the human intestinal microbiome and the production of fecal metabolites and their impact on the plasma metabolome. Omnivorous and vegan diets can alter fecal amino acid levels, supporting the growth of Firmicutes capable of amino acid metabolism. The impact of enteral nutritional therapy, particularly fiber, on the human microbiome influences metabolites that can modify health **[23]**.

In this sense, the authors Du et al. (2020) **[24]** performed a meta-analysis to analyze whether early enteral nutrition with probiotics can reduce mortality and infection rate in patients with severe craniocerebral injury, improve gastrointestinal function, and shorten the length of stay in the intensive care unit (ICU). A total of 39 studies involving 3,387 patients were included. Early enteral nutrition supplemented with probiotics was associated with a decreased risk of infection (pooled hazard ratio [RR], 0.486; 95% confidence interval [CI], 0.394-0.599), a decreased risk of mortality at 7, 14, and 28 days (pooled RR, 0.415, 0.497, and 0.385; 95% CIs, 0.196-0.878, 0.297-0.833, and 0.1970.751, respectively), and a decreased risk of gastrointestinal complications (pooled RR, 0.363; 95% CI, 0.274-0.481). It also shortened the recovery time of enteral function and shortened the length of hospital stay and the length of stay in the ICU (standardized mean differences, -3.327 and -1.461; 95% CIs, -6.213 to -0.440 and -2.111 to -0.811, respectively).

The authors Tian et al. (2022) **[25]** demonstrated that the gut microbiome of stroke patients is significantly altered and that the degree of microbiota disturbance correlates with prognosis. Enteral nutrition can remodel the gut microbiome and is important for stroke patients with dysphagia. A total of 17 healthy controls (HC), 54 stroke patients with oral feeding (OF) and 50 stroke patients with enteral nutrition were matched to investigate changes in gut microbiota with enteral nutrition in the first week after admission and dynamic changes. The relationship between the gut microbiome and clinical characteristics was investigated in a larger sample of participants who received enteral nutrition (n=147). Survival analysis was performed using Cox proportional hazards regression. The composition and structure of the gut microbiota were analyzed by 16S rRNA sequencing. Compared to the HC and AO groups, patients receiving enteral nutrition exhibited significantly different gut microbiota compositions in the first and second weeks. Therefore, the gut microbiota in ischemic stroke patients receiving enteral nutrition is significantly altered, and specific bacterial strains may be associated with prognosis and clinical indicators.

A randomized clinical trial compared the use of standard enteral formula versus enteral formula with prebiotic content in terms of nutritional therapy outcomes among neurocritical care patients. Forty-six adult neurocritical care patients who received nutritional therapy with standard enteral formula (SEF group; n=23) or enteral formula with prebiotic content (EFPC group; n=23) during their ICU stay were included. Data on patient demographics (age, sex), diagnosis, comorbidities, anthropometry, length of stay (LOS) in the hospital and ICU, Nutritional Risk Screening (NRS-2002) score, and Acute Physiology and Chronic Health (APACHE-II) score were recorded at enrollment. Data on daily nutritional intake, laboratory findings, complications, and drug treatments were recorded on Day 1, Day 4, Day 7, Day 14, and Day 21 of nutritional therapy in the SEF and EFPC groups. The use of EFPC compared to SEF was associated with significantly higher values of total energy, carbohydrates, proteins, lipids, enteral volume, and fluid intake (p-values ranged from <0.05 to <0.001) on each day of nutritional therapy. The target dose was achieved by most patients (86.9%) and by day 4 of nutritional therapy in most patients (71.7%) in the overall study population. Patients in the EFPC group had a non-significant trend toward a higher (95.7% vs. 78.3%) and earlier (87.0% vs. 56.5% on day 4) rate of target dose achievement, a lower rate (8.7% vs. 56.5%) and faster improvement (none vs. 52.2% had diarrhea on day 7) of diarrhea, and a lower insulin requirement (56.5% vs. 13.0%, $p = 0.002$). Nutritional therapy was associated with a significant decrease in prealbumin (Day 14 vs. Day 1, $p < 0.05$ for both), albumin (Day 14 vs. Day 1, $p < 0.01$ for SEF, $p < 0.05$ for PEF), hemoglobin (Day 14 and Day 21 vs. Day 1 and Day 14 vs. Day 4, $p < 0.001$ for each for SEF, Day 7, Day 14 and Day 21 vs. Day 1, $p < 0.01$ for each for PEF), and hematocrit (Day 14 and Day 21 vs. Day 1, $p < 0.001$ for each for both levels in the SEF and EFPC groups). Therefore, the findings revealed the achievement of target nutritional intake in most neurocritical patients through nutritional therapy, while EFPC was associated with a non-significant trend toward more frequent and earlier achievement of the target dose. along with a significantly lower rate and faster improvement of diarrhea compared with the SEF group. Pre-albumin and albumin levels remained below the normal range, while C-reactive protein (CRP) and white blood cells (leukocytes) were above the normal range throughout the nutrition period in both groups, while creatinine and urea levels were higher in the EFPC group than in the SEF group **[26]**.

Furthermore, maintaining adequate nutrition is crucial for people with Amyotrophic Lateral Sclerosis (ALS). Enteral tube feeding is offered to people with difficulty swallowing (dysphagia) to prevent weight loss and aspiration pneumonia. Among the types of enteral tube feeding, percutaneous endoscopic gastrostomy (PEG) is the typical procedure offered to ALS patients. Thus, the authors Sulistyo et al. (2023) **[27]** evaluated the effectiveness of PEG or other enteral tube feeding in ALS patients, compared to oral feeding without enteral tube feeding. No studies were found that randomized clinical trials indicating whether enteral tube feeding is effective compared to continued oral feeding for any of the outcome measures.

Other authors investigated through a retrospective study the role of nasal inspiratory pressure during a sniff (SNIP) at baseline in predicting PEG placement in ALS. Data from a clinical incident cohort of 179 ALS cases treated at the multidisciplinary ALS unit were included. At baseline, patients underwent detailed neurological, nutritional, and respiratory assessments, including SNIP and forced vital capacity measurements. Patients were then followed up approximately every three to six months until they were able to attend the center. During the follow-up period, 75 participants (42%) received PEG implantation. PEG placement was more frequent (57% vs. 31%; $p = 0.001$) and earlier (after 11.6 ± 14.0 months from the first consultation, vs. 23.3 ± 15.5 months; $p<0.0001$) in the group of patients with baseline SNIP ≤ 40cm H_2O. Baseline SNIP was a predictor of PEG placement even after correction for multiple potential confounders (HR 0.98; 95% CI: 0.96-0.99; $p = 0.02$) **[28]**.

In this respect, symptoms such as dysphagia, depression, cognitive impairment, difficulty with self-feeding and meal preparation, hypermetabolism, anxiety, respiratory failure, and fatigue during meals increase the risk of malnutrition in ALS patients. Malnutrition negatively affects prognosis and quality of life, making early and frequent nutritional assessments and interventions essential. Implementing an adequate caloric diet, modifying diet texture, using adaptive feeding utensils, and placing a feeding tube help prevent malnutrition. When nutritional status is compromised by dysphagia and weight loss (5%-10% of usual body weight) or body mass index <20 kg/m2 without weight loss, and when forced vital capacity is >50%, percutaneous endoscopic gastrostomy placement is indicated. When forced vital capacity is <50%, a radiologically inserted gastrostomy is the preferred method of enteral placement due to lower aspiration and respiratory risk. Parenteral nutrition is indicated only when enteral nutrition is contraindicated or impossible [29].

Finally, home enteral nutrition (HEN) is used to prevent or correct malnutrition in outpatients. A prospective, observational, multicenter study was conducted in 21 Spanish hospitals. Patients who received HEN via nasogastric tube or ostomy were included. 414 patients were included. Most of the diagnosed conditions were neurodegenerative diseases (64.8%). A total of 100 (25.3%) were diabetic. The mean weight was 59.3 ± 10.4 kg and BMI 22.6 ± 3.2 kg/m^2. Moderate protein-calorie malnutrition was predominant at the beginning of the study (46.4%). Improvement in nutritional status at six months was recorded in more than 75% of patients ($p<0.05$). Problems with tolerance, diarrhea, and abdominal distension decreased between the 3- and 6-month visits ($p<0.05$). Patients who received intermittent enteral nutrition had fewer tolerance-related effects (OR 0.042; 95% CI 0.006-0.279) and less diarrhea (OR 0.042; 95% CI 0.006-0.279) [30].

Conclusion

It was concluded that enteral nutrition supplemented with probiotics effectively reduces the risk of mortality, gastrointestinal complications, and infection, and shortens the length of stay in the ICU; therefore, it should be widely adopted for the management of these patients. Nasal inspiratory pressure during a sniff at the beginning of the study is an early indicator of disease progression and, therefore, of the need for enteral nutrition in amyotrophic lateral sclerosis. Furthermore, problems with intolerance, diarrhea, and abdominal distension decreased between the 3- and 6-month follow-up visits in patients who received home enteral nutrition.

CRediT

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Informed Consent

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Conflict of Interest

The authors declare no conflict of interest.

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Application of Artificial Intelligence (AI)

Not applicable.

Peer Review Process

It was performed.

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