Review Paper

Benefits of using oligomeric enteral formulas

Benefícios do uso de fórmulas enterais oligoméricas

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Aline Cattani[1]
Sérgio Henrique Loss[2]

ABSTRACT

Introduction: The high prevalence of enteral nutrition (EN) in hospital environments is a reality. However, common complications include gastrointestinal tract dysfunction and/or intolerance to EN. Thus, oligomeric formulas emerge as alternatives for the management of these conditions. The objective of this integrative review was to synthesize the literature on the composition of oligomeric formulas, their role in the care of adults and elderly patients, and the possible cost and efficacy implications of their use in clinical practice. **Methods:** A scoping review was performed on the potential benefits of oligomeric enteral formulas in patients requiring nutritional therapy. Google Scholar, MEDLINE, and PubMed were used to search for papers using "nutritional support", "enteral nutrition", and "oligomeric formulas" as keywords. The retrieved papers were assessed and used in the review according to their quality and methodology. **Results:** The composition of oligomeric formulas based on di- and tripeptides (mainly hydrolyzed whey protein) and medium-chain triglycerides facilitates their digestibility and absorption with lower intestinal O2 consumption. Nutritional interventions in critically ill patients with oligomeric formulas can manage the signs and symptoms of gastrointestinal intolerance, reduce episodes of hyperglycemia, reduce muscle loss and acquired weakness, improve caloric and protein supply, and reduce mortality and length of hospital stay. Promising results in other clinical conditions and in patients receiving home EN were also observed. Evidence of cost reduction with the effectiveness of oligomeric formulas has been identified, mainly because of the reduced use of health system resources with the control of EN intolerance. **Conclusions:** Considering that intolerance to EN is a reality in health services, an option for the early management of the patient's signs and symptoms is the use of an oligomeric formula because of its potential positive impact on clinical and economic outcomes related to the patient.

Keywords:
Nutritional therapy. Enteral nutrition. Oligomeric formulas.

RESUMO

Introdução: A alta prevalência de utilização de nutrição enteral (NE) no ambiente hospitalar é uma realidade. Porém, uma complicação comum é a disfunção do trato-gastrointestinal e/ou intolerância à NE. Dessa forma, as fórmulas oligoméricas surgem como alternativa para o gerenciamento destas condições. O objetivo da presente revisão integrativa é sintetizar a literatura acerca da composição das fórmulas oligoméricas, seu papel no cuidado do paciente adulto/idoso e as possíveis implicações de custo e eficácia do seu uso na prática clínica. **Método:** Foi feita uma revisão de escopo dos potenciais benefícios das fórmulas enterais oligoméricas em pacientes que necessitam de terapia nutricional. Foram realizadas buscas no Google Scholar, MEDLINE e PubMed, utilizando as palavras-chave: "suporte nutricional", "nutrição enteral" e "fórmulas oligoméricas". Os artigos identificados foram avaliados e utilizados de acordo com sua qualidade e metodologia. **Resultados:** A base da composição de fórmulas oligoméricas com di e tri-peptideos (principalmente proteína do soro do leite hidrolisada), bem como triglicerídeos de cadeia média, facilita sua digestibilidade e absorção, com menor consumo de O2 intestinal. Intervenções nutricionais em pacientes críticos com fórmulas oligoméricas têm potencial para manejo dos sinais e sintomas de intolerância gastrointestinal, redução dos episódios de hiperglicemia, menor perda muscular e fraqueza adquirida, melhor oferta calórica e proteica, bem como redução de mortalidade e tempo de internação. Resultados promissores em outras condições clínicas e em pacientes em NE domiciliar também foram observados. Evidências de redução de custo com a eficácia das fórmulas oligoméricas são identificadas, principalmente por conta da menor utilização de recursos do sistema de saúde com o controle da intolerância à NE. **Conclusões:** Considerado que a intolerância à NE é uma realidade nos serviços de saúde, uma opção para manejo precoce dos sinais e sintomas do paciente é a utilização de fórmula oligomérica, devido a seus potenciais impactos positivos nos desfechos clínicos e econômicos relacionados ao paciente.

Unitermos:
Terapia nutricional. Nutrição enteral. Fórmulas oligoméricas.

Address for correspondence:
Aline Cattani
Avenida Júlio de Castilhos, nº 2163, Centro - Caxias do Sul, RS, Brasil – CEP: 95010-000
Email: aline.cattani@hotmail.com

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1. Coordenadora do Serviço de Nutrição, Fonoaudiologia e EMTN do Pompéia Ecossistema de Saúde, Caxias do Sul, RS, Brasil.
2. Intensivista especialista pela AMIB, especialista em Terapia Nutricional pela BRASPEN, nutrólogo pela ABRAN e Coordenador da EMTN do Hospital de Clínicas e Hospital Moinhos de Vento, Porto Alegre, RS, Brasil.

INTRODUCTION

Malnutrition related to diseases in the hospital environment is highly prevalent in Latin American countries and can range from 40 to 60% at admission. These rates tend to increase over a longer hospitalization period, resulting in adverse health and economic impacts[1]. Considering the nutritional status of patients upon hospital admission, the intensive care unit (ICU), the inpatient unit, and discharge, nutritional therapy (NT) is a crucial component of patient-centered care. In addition to its impact on nutritional status, NT contributes to wound healing, reduction of the catabolic response to disease, preservation of gastrointestinal structure and function, and consequently, improves clinical outcomes of patients[2,3]. Thus, the recommendation of early NT is a consensus among several nutrition and intensive care societies in several countries, where it should be initiated in the first 24-48 hours of hospitalization for patients unable to maintain adequate oral intake (provided they are hemodynamically stable and have adequate gastrointestinal function), where the enteral route should be used as the first-choice option for offering NT[3]. According to the meta-analysis by Lewis et al.[4], which compared enteral nutrition (EN) and parenteral nutrition (PN), there was no difference in the outcomes of mortality, aspiration, and pneumonia between the two NT methods. However, the authors observed that EN reduced the incidence of sepsis.

The use of EN in the hospital environment is expected because of patients' clinical conditions, as well as the consequent difficulty in meeting nutritional needs with exclusive oral nutrition[5]. Furthermore, with advances in life support therapy, the use of home EN as part of medical care after hospital discharge has increased exponentially[6]. According to a systematic review, EN is effective in improving the quality of life reported by patients[7]. EN also contributes to maintaining intestinal integrity and modulating the physiological response to stress, because of the interaction between the intestine and the patient's immune system[8]. However, it is also essential to consider that approximately one-third of the patients who receive EN in hospital institutions have gastrointestinal intolerance[9].

From this perspective, critically ill patients using EN have an even higher frequency of gastrointestinal intolerance, which occurs mainly between the third and fifth days of NT. Signs of intolerance are associated with reduced nutritional intake (calories and proteins), as well as worse clinical outcomes, such as fewer days free of mechanical ventilation and prolonged ICU stay[10]. Furthermore, an increased number of symptoms of intolerance to EN is an independent predictor of mortality within 28 days[11]. Considering that the assessment of gastrointestinal tract function is still subjective, owing to differences in the definitions of signs and symptoms and associated biomarkers[12], a new tool called the Gastrointestinal Dysfunction Score (GIDS) was recently proposed to assess the degree of gastrointestinal tract dysfunction. The tool considers the absence of peristalsis, vomiting, residual gastric volume, gastrointestinal paresthesia (ileus), abdominal distension, diarrhea, gastrointestinal bleeding, intra-abdominal pressure, lack of oral diet, use of prokinetics, mesenteric ischemia, and/or abdominal compartment syndrome. The authors observed that GIDS was independently associated with 28 and 90-day mortality when evaluated alongside the Sequential Organ Failure Assessment (SOFA) in critically ill patients[13].

Gastrointestinal tract dysfunction should be constantly monitored in critically ill patients. Slow gastric emptying can delay the delivery of nutrients to the small intestine, which, when associated with intestinal hypoperfusion, potentially triggers a series of harmful events linked to changes in the digestion and absorption of nutrients and impairment of the intestinal barrier function. This is particularly debilitating in hypercatabolism scenarios[14,15]. Identifying, preventing, and managing EN intolerance can improve the nutritional supply to patients and clinical outcomes. In addition, the choice of enteral formula and its nutritional composition can directly affect the tolerance and absorption of the nutrients offered.

The objective of this integrative review was to synthesize the literature on the composition of oligomeric formulas and their role in the care of adults and elderly patients and verify the possible cost and effectiveness implications of their use in clinical practice.

METHODS

A scoping review of the potential benefits of oligomeric enteral formulas in patients requiring nutritional therapy was performed. The literature search was performed in May and August 2024. In Google Scholar, MEDLINE, and PubMed, the words "nutritional support", "enteral nutrition", and "oligomeric formulas" were used to search for articles. A manual search was also performed to review the references list of included articles. Studies were considered eligible if they reported a relationship between the use of oligomeric formula and clinical outcomes in patients aged >18 years. The retrieved articles were assessed according to their quality and methodology.

RESULTS

Composition and digestibility of oligomeric formulas

Several components of enteral formulas can affect gastrointestinal tolerance in patients[16]. In this context, oligomeric formulas are just as nutritionally complete as polymeric formulas, but their composition based on peptides and hydrolyzed nutrients facilitates their digestion and absorption[17]. The main difference between both formulas in relation to absorption is due to their composition. Polymeric formulas, based on polypeptides, require gastric proteolysis and consequent intestinal proteolysis, that is, the breakdown of proteins into amino acids or smaller peptides. On the other hand, oligomeric formulas, based on di- and tripeptides, are readily absorbed in enterocytes by the peptide transporter (PepT 1), which is present in the intestinal membrane and is responsible for its absorption mechanism[18,19]. PepT 1 plays a facilitating role in NT, because it allows oligopeptides to be used as nitrogen sources in EN. Furthermore, protein absorption from enteral formulas containing di- or tripeptides is significantly better than those containing free amino acids because of a highly selective absorption pattern is observed in mixtures with free amino acids. This difference can be attributed to the better transport capacity of oligopeptides (when compared to free amino acids), as well as the reduced osmolarity of the formula[18].

Another critical point is that the primary protein source of the oligomeric enteral formulas available on the market is hydrolyzed whey protein[20]. This protein stands out for its nitrogen composition, as it contains all the essential amino acids when compared to other protein sources, as well as approximately 26% branched-chain amino acids and 14% leucine[21].

Proteolysis and increased insulin resistance occur during acute illness. These factors, alongside immobilization and anabolic resistance, increase metabolic resistance of critical patients to any protein administration[21]. These events result in the establishment of a negative nitrogen balance and the depletion of muscle mass. Whey protein appears to be a good option for protein repletion in critically ill patients because of its better digestibility, resulting from shorter gastric emptying times. Considered as a fast protein, it reaches the small intestine in a shorter interval and consequently undergoes slower hydrolysis, allowing greater absorption[22]. It also has quicker and more effective peak in postprandial muscle protein availability. This occurs because leucine can directly activate the mTOR pathway, stimulating protein synthesis, reducing protein breakdown, and improving the patient's protein balance. Furthermore, the carbon skeleton of leucine is a precursor to beta-hydroxy-beta-methylbutyric acid (HMB), which can also stimulate muscle protein synthesis or possibly inhibit muscle protein degradation[21,23,24].

Another difference between polymeric and oligomeric formulations is their lipid compositions. Polymeric formulas are based on long-chain triglycerides. Their absorption requires emulsification with bile salts, lecithin, and cholesterol esters. This process aims to obtain the maximum surface area for digestion through lipolysis, which breaks triglyceride ester bonds and releases monoglycerides, free fatty acids, and glycerol. Once absorbed by enterocytes, fatty acids and monoglycerides undergo re-synthesis into triglycerides in the presence of ligase, coenzyme A, and adenosine triphosphate (ATP). Fatty acids are incorporated into chylomicrons, released into the lymphatic system, and transported to the blood and target organs. As they reach hepatocytes, they are transported to the mitochondria by the carnitine system[19,25]. Oligomeric formulas, on the other hand, have a higher percentage of shorter-chain lipids, such as medium-chain triglycerides (MCT). These are easier to digest, as MCT do not require bile salt emulsification or lipase hydrolysis. In other words, they are passively absorbed by enterocytes, directed to portal circulation, and transported to the liver. Without the need for the carnitine cycle for transport across the mitochondrial membrane, its availability for mitochondrial oxidation is better. Thus, they are an easier and faster energy source, and because of these characteristics, formulas with this composition are potentially important for managing patients with digestion and/or absorption disorders[25,26].

Oxidative stress associated with changes in tissue flow, with consequent dysoxia, also contributes to changes in intestinal permeability and the resultant impairment of digestive processes[15]. However, enteral NT can be administered to patients with hemodynamic instability using vasoactive drugs, including invasive hemodynamic devices[27]. According to the Brazilian guidelines for NT in critically ill patients, trophic EN in this condition can be considered cautiously, continually evaluating the signs and symptoms of intolerance[28]. In these cases, assessment of the vasopressor dose (stability, increase, or reduction), clinical signs, such as tissue perfusion and mottling, mean arterial pressure, and biochemical parameters, such as lactate, are essential for the success of NT[29,30]. One strategy for managing NT in these situations is to use a specialized enteral formula, such as a peptide-based formula, which minimizes intestinal O2 consumption for nutrient absorption[28,31].

The role of oligomeric formulas in patient care

Critical Ill Patients

The main scientific evidence available in the literature regarding the use of oligomeric formulas and their impact on patients is conducted in critically ill patients, as the incidence

of gastrointestinal intolerance can affect up to one-third of patients receiving EN[32]. It is challenging to manage this condition in the ICU setting because of the broad spectrum of pathophysiological mechanisms that affect different parts of the gastrointestinal tract results in a variety of signs and symptoms. In addition, the clinical outcomes of patients can be affected in several ways by intolerance itself, inadequate NT supply, and the impact of interventions[33]. As such, individualization and continuous reassessment of the dose and choice of enteral formula according to the phase of critical illness is recommended.

Large-scale clinical data comparing enteral formulas and feeding intolerance in critically ill patients are limited[34]. Table 1 reports the main studies available in the literature, many of which provide real-world experiences using oligomeric formulas and results in nutritional management in these patients.

According to the 2016 American Society for Parenteral Enteral Nutrition (ASPEN) guidelines, oligomeric formulas should be considered for managing patients with persistent diarrhea[35]. However, studies indicate that nutritional interventions with peptide- and MCT-based formulas have the potential to manage other symptoms of gastrointestinal intolerance and GRV[34,36-39], reduce episodes of hyperglycemia[34,40], reduce muscle mass loss and acquired weakness[36,41], improve caloric and protein supply[16,39,41-43], and reduce mortality[41,43]. Critically ill patients with acute gastrointestinal intolerance using oligomeric formulas were more likely to receive greater protein intake and have shorter ICU and hospital stay[39], though no benefit in mortality was demonstrated[39].

Five studies observed better protein supply with the use of oligomeric formulas[16,39,41-43]. Formulas based on hydrolyzed whey protein, with a higher leucine content

Table 1 – Studies with potential benefits of using peptide-based formulas in critically ill patients.

Author, year, location	Objective	Design, population	NT data	Key findings
Rice et al., 2019, USA and Canada[40]	Investigate whether a high-protein and low-carbohydrate peptide-based formula can facilitate glucose control and deliver higher protein concentrations	RCT, critically ill, overweight or obese (BMI 26-45 kg/m²).	Patients that required EN for 5 days or longer. Two groups: - High-protein peptide-based formula with 100% hydrolyzed whey protein and low-carbohydrate; - High-protein polymeric formula.	N=105 patients, 52 received peptide-based formula and 53 polymeric formula. Mean rate of glucose events >150 mg/dL decreased (p<0.05) and increased glucose control 80-110 mg/dL (p<0.001), without increasing glycemic events ≤80 mg/dL (p=0.23) and ≤60 mg/dL (p=0.94), in peptide-based formula relative to polymeric formula. Insulin administration decreased 10.9% (p<0.05) in peptide-based formula.
Nakamura et al., 2021, Japan[36]	Assess high-protein and medium-protein EN delivery under equal total energy delivery with and without active early rehabilitation with EMS.	RCT, critically ill patients ≥20 years.	Two groups: - Peptide-based formula (100% hydrolyzed whey protein) 1.8 g/kg/day and 20 kcal/kg/day; - Polymeric formula 0.9 g/kg/day and 20 kcal/kg/day. In both groups, there were periods of 10 days with and without EMS protocol.	N=117 patients, 60 in high protein group (median of 1.5 g/kg/day protein delivery) and 57 in medium-protein group (median of 0.8 g/kg/day protein delivery). Peptide-based formula group presented lower GRV (p<0.05). Femoral muscle volume loss was lower in peptide-based formula + EMS (p<0.005), as well lower proportion of PICS (p<0.05).
Azevedo et al., 2021 Brazil[41]	Evaluate the efficacy of high protein intake and early exercise versus standard nutrition care an routine physiotherapy on physical performance, ICU-acquired weakness and hospital mortality.	RCT, critically ill patients ≥18 years.	Two groups: - High-protein 2-2.5 g/kg/day (peptide-based formula hiperproteica with 100% hydrolyzed whey protein) + two daily sessions of cycle ergometry; - Medium-protein 1.4-1.5 g/kg/day (standard formula + routine physiotherapy protocol.	N=181 patients. The amount of protein received by the peptide-based formula (1.48 g/kg/day) was significantly higher than that received by the standard formula (1.19 g/kg/day) (p<0.0001). ICU (p<0.01), hospital (p<0.005) and 6 months (p<0.005) mortality were significantly higher in standard formula. ICU-acquired weakness was identified in 16 (28.5%) and 26 (46.4%) patients in the peptide-based formula and standard formula (p<0.05).

Continuation Table 1 – Studies with potential benefits of using peptide-based formulas in critically ill patients.

Author, year, location	Objective	Design, population	NT data	Key findings
Yamamoto et al., 2020, USA[16]	Evaluate the ability to meet nutritional needs with a calorically dense, peptide-based formula.	Prospective observational, critically ill patients ≥18 years.	Patients received a calorically dense, peptide-based formula with 100% whey protein for up to 5 days to assess the ability to achieve 50% of caloric and protein goals within the first 3 days (gradual increase).	N=25 patients. Percentages of patients who met at least 50% of caloric goal on days 1, 2, and 3 were 84%, 88%, and 79%, respectively; and who met at least 50% of protein goal were 76%, 79%, and 74%, respectively.
Seres et al., 2017, USA[38]	Compare the incidence of gastrointestinal intolerance to EN between polymeric formula and peptide-based.	Prospective randomized clinical comparison pilot study, critically ill patients ≥18 years.	Two groups: - High-protein peptide-based formula with hydrolyzed whey protein and casein; - High-protein polymeric formula; EN tolerance were evaluated up to 21 days, or until its discontinuation.	N=49 patients, 25 received peptide-based formula and 24 polymeric formula. Fewer days with adverse events (4.33 vs 9.92, p<0.05, OR=3.02), undesired gastrointestinal events (4.29 vs 7.13, p<0.05, OR=2.79) and fewer days with distention (0.88 vs 2.92, p<0.05, OR=3.75) observed in the peptide-based formula group as compared to the polymeric formula group.
Liu et al., 2016, Taiwan[37]	Compare peptide-based formula (with di and tripeptide) with a standard enteral formula in terms of tolerance and nutritional outcomes in surgical patients.	Retrospective cohort, critically ill patients with serum albumin concentrations ≤3.0 g/dL submitted to abdominal surgery.	Patients with EN for at least 7 days. Two groups: - Peptide-based formula with 78% hydrolyzed whey protein; - Polymeric formula.	N=72 patients, 32 received peptide-based formula and 32 polymeric formula. Lower average maximum GRV for the peptide-based formula group, compared to polymeric formula (p<0.05). There was no difference between the two groups in prevalence of diarrhea and pneumonia.
Ochoa Gautier et al., 2022, USA[43]	Determine the safety and clinical outcomes associated with early use of a very high protein and lower carbohydrate peptide-based in ICU.	Retrospective cohort, critically ill patients ≥18 years.	Data from the electronic medical records of ICUs in USA healthcare system. Three groups: - High-protein peptide-based formula hiperproteica (100% hydrolyzed whey protein >25% of TE); - High-protein formula (protein 21-25% of TE); - Standard formula (protein ≤20% of TE).	N=2.000 encounters As protein composition increased by type of formula, there was a reduction in 30 days mortality post-discharge (p<0.005). Patients receiving standard or peptide-based formula 21-25% TE had 2.5 (p<0.05) and 2.1 (p<0.05) odds of 30 days mortality, respectively, compared to patients receiving high-protein peptide-based hyperprotein >25% TE. High-protein peptide-based formula >25% TE group received more protein compared to the other groups (p<0.0001).
Wang et al., 2022, China[39]	Investigate the influence of peptide-based and polymeric formulas on the prognosis of critically ill patients with acute gastrointestinal injury.	Retrospective cohort, critically ill patients ≥18 years admitted to ICU for at least 7 days.	Two groups: - Calorically dense, high-protein, peptide-based formula; - Normoprotein-normocaloric polymeric formula.	N=192 patients, 71 received peptide-based formula and 121 polymeric formula. The amount of energy and protein received by the peptide-based formula was higher than that received by the polymeric formula. The use of peptide-based formula was the only independent variable of reduction in gastric retention and diarrhea (HR=0.469, p<0.05; e HR=0.394, p<0.05, respectively).

Introduction Table 1 – Studies with potential benefits of using peptide-based formulas in critically ill patients.

Author, year, location	Objective	Design, population	NT data	Key findings
ApSimon et al., 2020, Canada[42]	Assess the protein intake before and after availability of the high-protein peptide-based formula.	Retrospective cohort, critically ill patients ≥18 years.	Patients with EN exclusively for ≥ 5 days Two groups: - High-protein peptide-based formula (100% hydrolyzed whey protein); - Polymeric formula.	N=40 patients. The total protein delivered was significantly higher in the peptide-based formula group (1.46 g/kg/d), compared to vs the polymeric gormula group (1.1 g/kg/day) (p<0.005). The energy delivered was not significantly different between groups (p=0.901).
Nguyen et al., 2024, USA[34]	Verify patient characteristics, disease severity, and EN formulas in relation to feeding intolerance.	Retrospective cross-sectional, critically ill patients ≥18 years.	Database: PINC AI™ Healthcare from 2015 to 2019. Patients with EM for at least 3 days. Three groups: - Peptide-based formula (100% hydrolyzed whey protein); - Peptide-based formulas; - Polymeric formulas.	N=19.679 patients from 67 hospitals. Gastrointestinal intolerance was 18% higher for the other peptide-based group (n=3.121) and 15% higher for the polymeric group (n=13.316) compared with the 100% whey-peptide group (n=3.242) (p<0.05). In secondary analysis, odds of hyperglycemia were 81% higher for the other peptide-based group compared with the subgroup of very high-protein 100% whey-peptide (p<0.001).

N = sample size; BMI = body mass index; EMS = electrical muscle stimulation; EN = enteral nutrition; GRV = gastric residual volume; ICU = intensive care unit; PICS = persistent inflammation, immunosuppression, and catabolism syndrome; RCT = randomized clinical trial; TE = total energy; USA = United States of America.

(when compared to plant-based proteins), have easier intestinal absorption and a greater tendency to stimulate protein synthesis[22,44]. Furthermore, muscle depletion and malnutrition affect not only survival but also long-term recovery of critically ill patients, highlighting the importance of early interventions and consistent nutritional monitoring[45]. One point of focus is the use of protein modules to help achieve protein goals in critically ill patients. Therefore, it is necessary to assess the team's adherence to the correct administration of the modules and care when washing the tube to avoid obstruction. Despite the wide availability of modules in hospitals, Heyland et al.[46] observed that protein modules are used infrequently, contributing little to total protein intake.

In a Brazilian study by Azevedo et al.[41], ICU-acquired muscle weakness was observed in 16 (28.5%) and 26 (46.4%) patients in the oligomeric and standard formula groups, respectively ($p<0.05$). Although the significance is borderline, these data demonstrate a trend towards the development of ICU-acquired weakness in the control group. Using the oligomeric formula, the authors achieved a protein intake of 1.48 g/kg/day, compared to 1.19 g/kg/day in the standard formula group[41]. In the daily routine of intensive care teams, all these factors should be considered good practices in the assessment of EN supply since they directly impact the actual NT supply as prescribed by the health professional[42].

Nguyen et al.[34] e Rice et al.[40] similarly observed a correlation between the use of an oligomeric formula and better glycemic control in critically ill patients. Hyperglycemia, which is frequently observed in this patient profile, contributes to adverse outcomes. In this scenario, seeking enteral formulas that aid in this control adds to efforts to improve the outcomes for these patients[47]. Rice et al.[40] also explored a strategy of increasing the proportion of protein (100% hydrolyzed whey protein) while reducing carbohydrate loads in overweight and obese patients. The authors observed a reduction in hyperglycemic events, an increase in normoglycemic events, a reduction in mean serum glucose levels, and a lower need for insulin. Thus, there is a possibility for improvement in the nutritional management of patients as well as new methods for adequate glycemic control.

In summary, the advantages of using oligomeric formulas in critical care patients include improved protein absorption and nutritional status, reduced gastrointestinal complications, and potentially shorter ICU and hospital stay. These benefits make oligomeric formulas a valuable option for the nutritional management of critically ill patients.

Hospitalized Patients with Other Clinical Conditions

Clinical data evaluating the effect of oligomeric formulas and tolerance to EN are scarce in hospitalized patients with other clinical conditions, as shown in Table 2. A study that enrolled elderly patients with stroke showed an association between an oligomeric formula containing exclusively hydrolyzed whey protein and reduced inflammation and increased antioxidant defenses when compared to a formula containing hydrolyzed casein[48]. Hamaoui et al.[49] and Tiengou et al.[50] observed adequate tolerance of patients to the oligomeric formula, allowing progression of the estimated nutritional intake as planned at the beginning of the study. In patients with acute pancreatitis, the data suggest that the oligomeric formula could be associated with favorable clinical outcomes, such as less weight loss and shorter hospital stays (when compared to the polymeric formula)[50].

Possibly, the use of oligomeric formulas for some period will be advantageous in terms of better nutritional assimilation in patients with short intestine, decompensated inflammatory bowel disease, severe acute pancreatitis associated with intestinal malabsorption of nutrients, and refractory moderate-high output enteral fistula[51].

Patients Using Home Enteral Nutrition

During the patient's journey, in several situations after hospital admission or during hospitalization, it may be necessary to start EN and then, upon discharge at home, continue with the indication of using a feeding tube. Other patients may be identified as having nutritional risk and/or clinical indications at the outpatient level and may need to start EN[52]. In the United States, approximately 250,000 patients are estimated to receive home enteral nutrition[6]. In Brazil, according to data from the Brazilian Survey on Home Nutrition Therapy, most companies providing home care serve patients exclusively with ENT (67%). The higher prevalence of home NT is due to the increase in the elderly population, as well as the more significant presence of chronic diseases that result in longer hospitalization times, generating dependence and/or incapacity of the patient[53].

Given this scenario, Mundi et al.[54] assessed tolerance to oligomeric formulas in patients at risk of malabsorption.

Table 2 – Studies with potential benefits of using peptide-based formulas in hospitalized patients with other clinical conditions.

Author, year, location	Objective	Design, population	NT data	Key findings
Aguilar-Nascimento et al, 2011, Brazil[48]	Investigate the effect of a high-protein peptide-based formula on the levels of glutathione and inflammatory markers in aged patients with acute ischemic stroke.	RCT, aged patients ≥65 years with acute ischemic stroke	Two groups with early EN 35 kcal/kg/day and 1.2 g/kg/day of protein for at least 5 days: - Peptide-based formula (100% hydrolyzed whey protein); - Peptide-based (hydrolyzed casein).	Albumin levels dropped from the first to the fifth EN day only in the casein group (p<0.01). IL-6 decreased (p<0.05) and glutathione increased (p<0.05) only in the hydrolyzed whey protein group.
Hamaoui et al., 1990, USA[49]	Evaluate tolerance to a peptide-based formula in the immediate post-operative period and compare it with PN in relation to nutritional effectiveness and cost.	Prospective randomized clinical comparison, patients undergoing abdominal surgery.	Two groups of postoperative NT: - EN with peptide-based formula (jejunum); - PN.	N=19 patients, 11 receiving peptide-based formula and 9 PN. EN with peptide-based formula was well tolerated, allowing achieve planned progression within the first 3 days. The cost of EN was lower compared to PN. Both groups had positive caloric balance. However, in peptide-based formula group lower caloric intake was delivered compared to PN.
Tiengou et al., 2006, France[50]	Compare a peptide-based formula to a polymeric formula in patients with acute pancreatitis in terms of tolerance and the impact on the clinical outcome.	Randomized prospective pilot study, patients with acute pancreatitis.	Two groups with EN via jejunum with similar caloric and protein content: - Peptide-based formula; - Polymeric formula.	N=30 patients, 15 receiving peptide-based formula and 15 polymeric formula. Adequate tolerance in both groups. Peptide-based formula use was associated with shorter hospital stay (p<0.05). Patients receiving peptide-based formula lost less weight compared to those with the polymeric formula (p<0.01).

N = sample size; EN = enteral nutrition; NT = nutrition therapy; PN = parenteral nutrition; RCT = randomized clinical trial; USA = United States of America.

A total of 95 patients were included in the study, of which 53 started home NT with oligomeric formula and 42 started with a polymeric formula and, due to intolerance, transitioned to an oligomeric formula. Patients who begun NT using an oligomeric formula showed no intolerance. In the transition group, the frequency of nausea and vomiting decreased from 42% to 22% ($p<0.05$), diarrhea decreased from 46% to 25% ($p<0.01$), and abdominal pain decreased from 22% to 5% ($p<0.01$). In addition, it was possible to achieve estimated nutritional goals for patients using the oligomeric formula. LaValle et al.[55] also evaluated gastrointestinal tolerance and described the clinical characteristics of adults receiving EN at home before and after starting an oligomeric formula with 100% hydrolyzed whey protein. A total of 1,022 patients were analyzed, and after starting the use of the oligomeric formula, a lower incidence of nausea and vomiting ($p<0.001$), diarrhea ($p<0.001$), constipation ($p<0.001$), gastric residue ($p<0.005$), and abdominal distension ($p<0.001$) was observed. In addition, the rate of patients with one or more intolerance events decreased from 59.0% to 41.2% ($p<0.001$) after using the oligomeric formula. These data provide essential information for healthcare professionals in decision-making, as low tolerance to EN may be an additional unfavorable factor for patient admission to home care programs and may even prolong their hospital stay.

There is no standard approach for treating gastrointestinal intolerance, especially in home EN patients. In both hospital and home settings, the flow rate of EN is expected to be reduced to reduce symptoms before restarting EN. However, this approach corroborates the exacerbation of malnutrition, owing to the low nutritional intake offered to patient[53]. It is worth noting that, in critically ill, hospitalized patients, as well as in patients receiving home EN, robust randomized clinical trials evaluating the effects of oligomeric formulations on clinical and nutritional aspects are still needed[39].

Cost and Effectiveness Implications of Oligomeric Formulations

In addition to the clinical benefits that oligomeric formulas can bring to patients, it is necessary to evaluate the economic impact of this transition. Mundi et al.[54], in addition to signs of intolerance, also assessed the financial implications of the transition from polymeric to oligomeric formula in patients who presented intolerance to EN. When comparing the situation before and after the transition, better results were observed regarding the use of health resources related to EN tolerance. After starting the oligomeric formula, there was a reduction from 1.8 ± 1.6 to 1.1 ± 0.9 in the number of calls to health services due to intolerance to EN ($p<0.01$). The mean number of emergency room visits due to aspects related to home EN decreased from 0.3 ± 0.6 to 0.09 ± 0.3 ($p<0.05$). The mean number of scheduled visits by home care providers decreased from 1.3 ± 1.3 to 0.3 ± 0.5 ($p<0.0001$). Corroborating these data, LaValle et al.[55], in the period before using the oligomeric formula, reported that 100% of patients registered at least one hospital visit. After the transition to the oligomeric formula, this rate was reduced to 72.1% ($p<0.01$). In these analyses, cost modeling revealed that outpatient visits represented the largest portion of healthcare costs after the first 30 days of starting the oligomeric formula.

Curry et al.[56] developed a cost-consequence model to compare total ICU costs for patients with and without GI intolerance receiving EN. The aim was to quantify the economic impact of the early use of an oligomeric formula compared to a standard polymeric formula. It was considered that 31 of the 100 patients who received EN had GI intolerance, requiring a mean ICU stay of 14.4 days, compared to 11.3 days for patients without GI intolerance. The model calculated that the oligomeric formula was more economical than the standard formula, as three cases (7%) of GI intolerance were avoided, resulting in cost savings through reduced ICU stay[56]. In another cost-effectiveness study, considering critically ill patients at high risk of gastrointestinal intolerance, a decision tree diagram model was developed for cost analysis. The objective of this study was to compare the cost of early use of oligomeric formula in the ICU with the standard polymeric formula of the Ministry of Health in Malaysia. To calculate the cost of the model, the average cost of each type of formula and the daily cost of ICU admission were considered. The authors suggested that replacing the standard polymeric formula with the oligomeric formula could reduce costs by US$216 per patient and US$1.7 million per year for the health system. The additional cost related to a longer hospital stay, due to gastrointestinal intolerance, was of US$1,114 per patient[57].

In a single-center retrospective analysis of population-based data from the Mayo Clinic Rochester of patients receiving home EN, Elfadil et al.[58] also evaluated the cost of transitioning to an oligomeric formula for the treatment of gastrointestinal intolerance. The authors observed that the prevalence of gastrointestinal intolerance decreased from 43.3% (four weeks before transition) to 21.6% after the initiation of the oligomeric formula. In addition, the average total care cost per patient decreased from $38,744 (four weeks before transition) to $21,129 (eight weeks after transition to the oligomeric formula). The trend toward reduction in healthcare utilization costs was consistent across emergency department visits, inpatient care, and outpatient care-related costs[58].

These findings are important because the cost of the oligomeric formula may be higher than that of the polymeric one. However, healthcare professionals must assess the costs

associated with gastrointestinal intolerance, including medications used to manage symptoms, outpatient consultations, and the use of healthcare services (consultations and/or hospitalization)[54].

CONCLUSION

EN intolerance is a reality in health services, and it is up to the professionals involved in the assessment and comprehensive care of the patient to consider the best NT for managing symptoms. Considering the negative impact on a patient's clinical outcome, identifying patients at potential risk of developing gastrointestinal tract dysfunction and/or intolerance to EN is essential for patient care. In this scenario, oligomeric formulas are viable alternatives, potentially benefiting patients' clinical outcomes. In addition to the clinical impact, it is necessary to consider the costs associated with managing gastrointestinal intolerance, such as medication use, prolonged hospitalization time, and related complications. In critically ill patients, given the hemodynamic impact of the acute phase of the disease, an oligomeric formula can be used to nourish and prevent complications associated with gastrointestinal intolerance. Therefore, early transition to an oligomeric formula should be considered as soon as the patient is identified as having a high risk of malabsorption and/or intolerance to the polymeric formula.

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