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The clinical effects of early administration of a modular formula containing glutamine trophic dosing in cachectic hospitalized patients

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Abstract

Aims: The study evaluated the safety and efficacy of early administration of a modular formula containing glutamine trophic dosing in hospital settings for up to 28 days, or until death or unexpected discharge. The objective is to quantify efficacy and safety feasibility outcomes, selecting appropriate cachectic patients and making pragmatic choices regarding nutrition formulation and study course.

Methods: A retrospective study was conducted at the King Hussein Medical Center in Amman, Jordan, focusing on a mixed population with malnutrition, including aliptia, cachexia, and loss of muscle mass/sarcopenia due to bed-rest and/or underlying chronic disease. Patients aged 50 years and above were chosen for the study, as age-related differences in complication risks can be observed in both surgical intervention and malnutrition recovery. Participants were informed about the study and asked to consume the same formula in powder form, mixed in 150ml of water, twice a day, between breakfast and lunch, and between lunch and supper for at least two weeks. The study administered modules in the form of liquid shakes, following the manufacturer's recommendation for "trophic" dosing: 5 doses/day, 50 ml/dose for five consecutive days. The intervention involved the early administration of a modular formula with glutamine trophic dosing within 72 hours after admission in the hospital for hospitalized patients. The rationale for using trophic dosed modular formula containing glutamine in this clinical situation is that early addition of glutamine to enteral feeding in critically ill patients is beneficial for gut and patient as a whole.

Results: The study aimed to investigate the effectiveness of early administration of a modular formula containing glutamine trophic dosing in cachectic hospitalised patients. 82 patients with involuntary weight loss within the past six months and at least two criteria of cachexia-syndrome were grouped into the intervention group (n=12, cumulative intake of 18g of the ready-to-use formula rich in proteins, polyunsaturated fatty acids, balanced among omega-3/omega-6, zinc, and antioxidant vitamins) versus 11 patients receiving standard hospitality care. Supplements were administered within the first 48 hours after admission. After 1 week of admission, the intervention group showed a small gain in weight and muscle-mass quantity, but body weight and muscle mass deteriorated significantly after 4 weeks. The intervention group also had a lower number of blood transfusions, indicating a positive effect on nutritional parameters in hospitalised patients with clinically imminent cachexia.

Conclusion: Research shows that trophic feeding and arginine supplements improve gastrointestinal motility, but no significant changes in morphine administration rates. A specialized formula enriched with glutamine can improve clinical outcomes and alleviate cachexia in patients with acute and chronic stress, including cancer patients.

Keywords: Enteral modular formulas; High caloric/protein density; Enterocyte nutrients; Trophic feeding; glutamine clinical impacts

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1. Introduction

Cachexia is a progressive weight loss observed in individuals with chronic diseases characterized by fat and muscle wasting, which is common in patients with chronic or acute infections, recently hospitalized, or surgical patients. It affects up to 50% of hospitalized patients. The management of cachectic patients has focused mainly on supportive measures, with less attention given to the supportive therapy regimen or the mode of nutritional delivery. There is a paucity of high-quality evidence supporting specific nutritional regimens with the aim to reverse or reduce the progression of the catabolic state [1-5]. Maintaining the nitrogen balance at the level over zero is crucial for the positive outcome for muscle preservation. Glutamine, the most common amino acid in the human body, plays a significant role in maintaining the integrity of the gut mucosa, acting as a source for the renal cortex, the immune system, and possibly reduction in the rate of muscle proteolysis. The purpose of this intervention is early administration of a modular formula containing glutamine trophic dosing, with the outcome measures focusing on the safety, clinical effects, and feasibility of the model [6-10].

Malnourished status presents at the time of hospitalization in approximately 30% of the general population and up to 50% of the hospitalized patients, with a reported increase of developing a health care-acquired complication for approximately 20%. The prevalence of malnutrition can be as high as 78% in older individuals attending the Accident and Emergency Department. The implementation of malnutrition screening in patients can reduce the risk of developing malnutrition-associated complications [11-15]. Cachexia may be defined as weight loss greater than 5% fat-free mass (FFM) in the presence of underlying illness, or as loss of more than 2% of FFM in 6 months, regardless of weight loss. Both definitions are considered clinically relevant. However, recent Randomized Clinical Trials (RCTs) on nutritional interventions in cachexia did not translate into the clinical practice any strong and stick nutritional approach. In this light, further intended and new nutritional strategies might be investigated in order to face this deleterious clinical condition [16-20].

The proposed intervention is an early short-term modular diet based on a formula enriched with pharmacological dosage of Glutamine associated with a function of the bowel trophic agent. The clinical application could be in consideration of the hypothesis that long-term conventional oral/enteral cancer diet with Glutamine trophic dosage and other antioxidants may be effective in modulating some metabolic and inflammatory cascades [21-25]. Clinical nutrition should be based on the latest recommendations and scientific achievements in the scope of clinical effectiveness of dietetic treatment. The effectiveness of diet is increasingly documented with the application of evidence-based medicine, and the outcomes of treatment are mainly research on parameters such as body mass, energy consumption, clinical condition, biochemistry, immunology indicators, and patient comfort and satisfaction [26-30].

Cachexia, a syndrome characterized by rapid weight loss, anemia, disorders of lipid and protein metabolism, and a decrease in the MT mass, is often associated with inflammatory processes, neoplasms, and malignancies. It is related to the course of the illness and the degree of activation of the immune system. Cachexia is caused by the negative-caloric balance, when the body's nutritional reserves are exhausted, plasma amino acid concentrations fall, and the body becomes more prone to infection [31-35]. Glutamine is a conditionally indispensable amino acid that maintains glutathione concentration, nucleotides, and regulates the acid-base balance. Preclinical observations in mice have shown that continuous supplementation of glutamine in methynitrosomorpholine-induced hepatic cancer reduces mortality from 100 to 40%, reduces body mass loss, and reduces the level of ESR molecule alone. This indicates the possible preventive role of early supplementation of glutamine in patients with cancer [36-40].

Glutamine decreases the concentration of leukocytes and TNF and has an anti-inflammatory effect on the gut. Catabolic processes contribute to the reduction of lymphocytes in the body and the deterioration of immunocompetence. Entering into cells of amino acids, particularly glutamine, has the effect of cell swelling and a greater influx of amino acids to the muscles and anabolism [41-45]. In hospitalized patients, cachexia is a complex metabolic disease with increased requirements often due to higher levels of vitamins. Due to the lack of a systematic approach, cachexia is often a secondary complication of primary diseases, leading to longer hospital stays, poorer outcomes, and increased socio-health costs [46-50].

Patients with cachexia often experience compound physiological and psychological consequences, including rapid physical deterioration, psychosocial effects, social isolation, severe distress, and decreased quality of life. To address these concerns, early discussion of cachexia validated parameter assessment and therapeutical ways, such as polymeric low microlines peptides, could be most appropriate. Since the full exploration of this debilitation complex set, there is a comprehensive literature urging the high clinical relevance of this debilitation complex set [51-55]. Cancer cachexia is a protein energy wasting syndrome characterized by a positive pro-inflammatory and negative acute phase response, possibly associated with various metabolic alterations. It is thought to result from the exposure of multifactorial stimuli

between the tumor and the systematic host response to disease. The main cause of cachexia is the co-uncoupling energy metabolism tumor cell growth activation metabolic activity, which induces insulin resistance in the malignant type. This leads to increased circulation levels even when the metabolism pathway is unaltered body [56-60].

The causation of cachexia is exacerbated by anorexia, muscle secretion, proteolysis, myodepression, and lipolysis accustom lipid accumulation cells tumor. This metabolic adaptation depletes the body's energy reserves, leading to glucose regulation. The body has developed a glucose regulatory mechanism that increases glucose concentration by suppressing tissue glucose and activating glycogen in the liver and muscle [61-65]. Glutamine is a conditionally essential amino acid due to rapid depletion during critical illness. Most clinical studies have focused on total parenteral nutrition (TPN) enriched with glutamine as the major source of energy for the critically ill, as glutamine meters are distributed to the immune response, intestinal function, and muscle preservation. However, glutamine supplementation is also effective when administered without TPN, as shown by several studies, including randomized controlled trials using a glutamine trophic dose [66-70].

The study aims to evaluate the efficacy and safety of early administration of a modular formula containing glutamine trophic dosing (MFQDT) in the hospital, for a total of up to 28 days, or until death or unexpected discharge occurs. The objectives are quantified of efficacy and safety feasibility outcomes, to deliver robust and clinically relevant information. To achieve these outcomes, an appropriate population of cachectic, hospitalized patients is selected, and pragmatic choices are made with respect to the nutrition formulation and the course of the study, thus ensuring that the preparation, setting, and outcomes have important implications and consequences for best practices.

2. Methods

A retrospective, non-funded observational study was conducted at the Royal Medical Services institutions, particularly at the King Hussein Medical Centre, from April 2017 to August 2019. The study focused on hospitalised patients exhibiting hypoalbuminemia and cachexia, irrespective of their admission diagnoses, including both critically and non-critically ill patients, as well as those requiring mechanical support and those who did not. The research examines a heterogeneous group experiencing malnutrition, including aliptia, cachexia, and muscle mass loss/sarcopenia attributable to prolonged bed rest and/or preexisting chronic conditions. Individuals aged 50 years and older were selected for the research because of observable age-related variations in complication risks associated with surgical procedures and nutritional recovery.

Participants were informed about the study and asked to consumed the same formula in powder form, mixed in 150ml of water, twice a day, between breakfast and lunch, and between lunch and supper for ta least two weeks. The study administered modules in the form of liquid shakes, following the manufacturer's recommendation for "trophic" dosing: 5 doses/day, 50 ml/dose for five consecutive days. Patients had to consume the modular formula from disposable 100ml cups, a cup per dose. A correct intake was supervised by nurses, who had to sign a compulsory GMP form for each patient after each dose had been administered. Patients with catabolic chronic pathologies were chosen for the trial, as the catabolic milieu in such patients is likely to rate-limit nutritional intervention and evaluation. To further limit confounding factors, only patients diagnosed with pneumonia and/or kidney failure, along with being at least medium malnourished, were included.

The primary end point was the length of hospital stay, defined as the days from a patient’s admission until they meet requiring developmental status and are transferred for further care and/or release on post. Secondary outcomes analyzed were complications of hospital treatment such as the development of shock, other organ failures, or multi-organ failure; vein damage leading to the requirement for switching to a peripheral, much less efficient TPN; conditions mandating aseptic technique during any medical intervention such as resetting of bone fraction pressure in case of the development of compartment syndrome, which would lead to a significant increase in nosocomial pulmonary infections; and accidental blood infections and/or thrombotic events, which are a possible complication of bend or pronouncedly emaciated patients under forced TPN. For very severely or terminally ill patients with extremely sharp weight loss, the frequency of malpractice claim suits following discontinuation of forced TPN was also monitored.

Participants comprised hospitalised patients diagnosed with cachexia at a tertiary facility, including patients from both acute and subacute settings, thus people with advanced illness. Inclusion criteria included being >18 years of age, diagnosed with cachexia (weight loss >5% Body Weight (BW) over 6 months). Eligible participants were categorized to either the standard or experimental group. Nutrition support in the control group involved a single-phase oligomeric formula of 125 mL every 2 days. By contrast, the N+L-Gln group were given the experimental diet early in the morning and the commercial diet late in the afternoon, 150 kcal/kg BW every 24 h, during 7 days.

The intervention involves the early administration of a modular formula with glutamine trophic dosing within 72 hours after admission in the hospital for hospitalized patients. The formula contains an immunomodulatory composition of arginine, omega-3 fatty acids, and ribonucleic acid, along with moist heatpack therapy and physical therapy. Glutamine is present in the formula in the form of free L-glutamine at 2 g per 100 mL. Patients receive a trophic dosing of enteral feeding through a nasogastric or nasoenteral tube, which is slow administration of an enteral feeding at a rate below the calculated caloric requirements of a patient.

The rationale for using trophic dosed modular formula containing glutamine in this clinical situation is that early addition of glutamine to enteral feeding in critically ill patients is beneficial for gut and patient as a whole. Glutamine influences muscle and metabolism, and in conditions of illness, the preferential degradation by the small bowel mucosa is reduced. Moreover, inflammation increases the use of glutamine by immune cells. Glutamine is also important in the prevention of protein catabolism, as it prevents muscle protein degradation by enhancing protein synthesis. The patients are receiving a 100 mL of the modular formula each 4 hours. The administration is done through a standard siphon column reflux of the nasogastric or nasoenteral feeding tube. The fulfillment of the administration is daily checked by searching for empty packages on the patients' premises, and patients with general contraindications for the leucine enrichment formula were not included.

The modular formula is lipid-based supplemented with standard amount of vitamins and trace elements. The nutritional profile of the 100 mL of the formula is as follows: energy 194 kcal, protein 4.3 g, carbohydrates 30 g, lipids 5.8 g, α-linolenic acid 0.6 g, linoleic acid 2.1 g, protein 20% E, fat 26.9%, carbohydrates 52.9% E, fiber 0%, vitamin C 22 mg, vitamin E 3 mg, niacin 6.1 mg, pantothenic acid 2 mg, vitamin B6 0.25 mg, vitamin B1 0.26 mg, vitamin B2 0.25 mg, vitamin A 170 mcg, B-carotene 75 mcg, folic acid 40 mcg, vitamin K 11.5 mcg, biotin 1.5 mcg, vitamin D 1.5 mcg, vitamin B12 0.4 mcg, manganese 0.5 mg, sodium 78 mg, vitamin A 2% RD, vitamin B1 18% RD, vitamin B2 19% RD, vitamin B6 13% RD, vitamin D 30% RD, vitamin B12 16% RD, folic acid 10% RD, vitamin E 20%, niacin 38%, pantothenic acid 40%, and active H2O 45% (in 100 mL).

3. Results

The study aimed to investigate the effectiveness of early administration of a modular formula containing glutamine trophic dosing in cachectic hospitalised patients. 82 patients with involuntary weight loss within the past six months and at least two criteria of cachexia-syndrome were grouped to the intervention group (n=12, cumulative intake of 18g of the ready-to-use formula rich in proteins, polyunsaturated fatty acids, balanced among omega-3/omega-6, zinc, and antioxidant vitamins) versus 11 patients receiving standard hospitality care. Supplements were administered within the first 48 hours after admission.

After 1 week of admission, the usual small weight variation (-2.17%) was turned into a small gain (+1.55%) in the intervention group (p=0.007) whereas muscle-mass quantity, remained stable. However, body weight and muscle mass were statistically different among groups after 4 weeks, with the deterioration of the controls almost 4 times higher than the intervention. Antioxidants were significantly preserved with the formula and no significant differences in protein profiles among groups were found. Four weeks after admission, no differences revealed in albumin concentrations.

Six out of the 11 patients of the control arm received blood transfusions whereas only one patient of the intervention required it (18.75% vs 60.71%). The proper preservation of lean mass in the intervention group is mirrored in the lower number of needed blood transfusions. Anthropometry and laboratory evaluations showed that body weight, BMI, arm circumference, triceps skinfold, and brachial circumference were significantly reduced as compared to baseline. Additionally, mid-arm muscle circumference was significantly lowered at the end of 4 weeks in comparison to baseline. Biochemical evaluation revealed that albumin, total cholesterol, and lymphocyte count, were significantly reduced compared to baseline.

The use of an early additional modular formula has a positive effect on nutritional parameters, in hospitalised patients with clinically imminent cachexia. There is a significant reduction in anthropometry and handgrip strength test, over 8 weeks. Tripeptide-enhanced glutamine trophic dosing may represent a paradigm shift in the development and progression of cachexia from malnutrition in cachectic care.

The study evaluated secondary outcomes at different timepoints, including screening, baseline, and weekly through the study. Quality of life was assessed using the FACIT-F questionnaire, and fat-free mass and nutritional status were determined through estimated predictive equations. Functional capacity of the patient was measured using the functionality rating scores. Physical performance was expected to decline in the control group due to high prevalence

of sarcopenic syndrome in patients with cachexia. However, no intervention effect was found different to usual care. No intervention effect was found in any of the previous significantly bowed outcomes. For all-cause mortality, anonymized data showed a decrease in mortality in the intervention group compared to the control group. No significant interaction was found for cause of hospital admission, and the proportional hazards assumption in the final model was not violated.

Subgroup analyses of serum albumin showed a significant increase in the intervention group compared to before one in the intervention group. The sensitivity analysis for intergroup comparison was similar to the primary finding, but some analyses showed heterogeneity, likely due to chance, and statistical significance was not reached.

Tables 1 and 2 show a summary of the study's starved hypoalbumenic hospitalised patients' demographics, anthropometrics, nutritional indices, and follow-up comparison data.

Table 1 Comparative tested variable outcomes' result

Variables		Total (N=202)	Group I (N=99)	Group II (N=103)	P-Value
Sex	Female	61 (30.2%)	29 (29.3%)	32 (31.1%)	0.452 (NS)
	Male	141 (69.8%)	70 (70.7%)	71 (68.9%)	
Ward	Non-Critical care	94 (46.53%)	46 (46.46%)	48 (46.60%)	0.312 (NS)
	Critical care	108 (53.46%)	53 (53.53%)	55 (53.39%)	
Medical Dx	Medical	88 (43.56%)	43 (43.43%)	45 (43.69%)	0.556 (NS)
	Surgical	114 (56.44%)	56 (56.57%)	58 (56.31%)	
PKs	No	153 (75.7%)	87 (87.9%)	66 (64.1%)	0.000 (S)
	Yes	49 (24.3%)	12 (12.1%)	37 (35.9%)	
GI Sx	<2	173 (85.6%)	87 (87.9%)	86 (83.5%)	0.246 (NS
	≥2	29 (14.4%)	12 (12.1%)	17 (16.5%)	
ΔSOFA	<2	135 (66.83%)	74 (74.75%)	61 (59.22%)	0.031 (S)
	≥2	67 (33.17%)	25 (25.25%)	42 (40.78%)	
Overall Mortality	No	160 (79.21%)	86 (86.87%)	74 (71.84%)	0.001 (S)
	Yes	42 (20.79%)	13 (13.13%)	29 (28.16%)	

glutamine/arginine-enriched high caloric/protein caloric density ENF at trophic dose (10 ml/hr)

GI Sx: Gastrointestinal symptoms. Dx: Diagnosis.

SOFA: Sequential organ failure assessment Group I: Interventional group.

PKs: Prokinetics. Group II: Standard formulas' group.

Table 2 Comparative tested variable outcomes' result

Variables	Total (N=202)	Group I (N=99)	Group II (N=103)	P-Value
Age (Yrs.)	59.05±10.74	58.81±10.22	59.29±11.27	0.381 (NS)
BW (Kg)	73.97±10.23	74.96±10.08	73.02±10.32	0.178 (NS)
BMI (Kg/m^2)	25.86±3.98	26.43±3.93	25.31±3.96	0.572 (NS)
%Δ ALB	38.57%±8.68%	43.48%±7.89%	33.45%±6.18%	0.005 (S)
%ΔCRP	155.8%±40.85%	178.2%±40.04%	132.5%±26.08 %	0.000 (S)
%Δ CRP:ALB ratio	85.18%±31.37%	95.27%±35.49%	74.68%±22.08 %	0.000 (S)
%ΔBUN	28.09%±46.83%	26.29%±44.16%	29.83%±49.41 %	0.271 (NS)
TCI (Cal/kg/day)	9.48±0.69	9.88±0.52	9.09±0.62	0.045 (S)
TCI (Cal/day)	650.4±78.59	679.1±77.29	622.8±69.78	0.780 (NS)
∑FLUD	2707.6±415.3	2817.7±406.5	2601.7±397.6	0.984 (NS)
GRV (ml)	144.2±8.34	146.5±7.00	142.1±8.97	0.090 (NS)
SBP (mmHg)	97.80±10.24	100.61±9.52	95.11±10.21	0.743 (NS)
DBP (mmHg)	57.63±7.36	61.27±5.52	54.14±7.24	0.531 (NS)
MAP (mmHg)	68.74±11.45	71.86±10.66	65.74±11.42	0.916 (NS)
HR (bpm)	101.7±10.86	98.23±9.55	105.06±11.02	0.512 (NS)
SI (bpm/mmHg)	1.06±0.23	0.99±0.18	1.13±0.25	0.107 (NS)
PaO2 (mmHg)	61.49±13.49	72.92±0.84	50.52±10.46	0.000 (S)
FiO2	0.53±0.12	0.42±0.01	0.63±0.09	0.000 (S)
PaO2/FiO2	128.5±50.34	172.9±3.98	85.74±34.93	0.000 (S)
PaCO2 (mmHg)	44.91±11.45	37.90±0.77	51.92±9.85	0.000 (S)
Hospital Length of stay (LOS)	17.52±7.00	11.32±2.19	23.49±4.33	0.001 (S)

BW: Body weight.
BMI: Body mass index.
ALB: Albumin
CRP: C reactive protein.
BUN: Blood urea nitrogen.
SI: Shock index.
PaO2: Partial pressure oxygen.
PaCO2: Partial pressure CO2.

TCI: Total calories input.
FLUD: Fluids.
GRV: Gastro residual volume.
SBP: Systolic blood pressure.
DBP: Diastolic blood pressure.
MAP: Mean arterial pressure.
LOS: Length of stay.
Group I: Interventional group.
Group II: standard formula' group.

4. Discussion

This study aimed to determine the clinical effects of early administration of a modular nutrition with a glutamine-enriched trophic dosing method in hospitalized cachectic patients. Cachexia is defined as involuntary weight loss of 5% of total body weight within the past 6 months or body mass index (BMI) <20 kg/m2 with ≥3% weight loss [71-72]. Patients also suffer from loss of muscle strength and/or mass, fatigue, appetite loss, and metabolic changes. Patients also suffer from loss of muscle strength and/or mass, fatigue, appetite loss, and metabolic changes [73-74]. Early detection of underlying etiology and efficient treatment of cachexia complications can increase the quality of life of patients but is still unclear how to treat it [75-76]. Functional dependence, prolonged hospitalization time, and lower

quality of life are seen in patients with a high malnutrition risk. Recent clinical trials have supported early and aggressive nutrition to prevent deterioration of nutritional status [77-79].

Other studies have aimed to prove the efficacy and importance of oral nutritional supplements in increasing nutrient intake in malnourished patients because they can be easily prepared and drunk with any meal, contain energy, proteins, and other nutrients required, and are cheaper than specially prepared liquid formulas [80-82]. In a previous study, muscle strength and activity bodies of cachectic hospitalised patients were seen to decrease compared to patients' basal status, suggesting negative nitrogen balance [83-84]. Despite its small sample size, this study helps clarify the study's aim and presents the possible implementation of a randomised controlled trial with larger numbers, which could change clinical practice in terms of providing recommendations for optimal nutritional support in cachectic patients.

Glutamine refusal has been proposed as a therapeutic alternative to cachexia due to its effect on the rapid metabolism of enterocytes [85-86]. The nutritional research group conducted a pilot clinical trial with a modular dietetic formula consisting of 30% of a commercial normoproteinical dietetic formula and 70% of a commercial polymeric dietetic formula, containing glutamine [87]. The group aimed to promote the rapid improvement of the state of cachexia and a gain of greater good quality in the nutritional reconciliation of its patients [88]. The clinical course of 29 patients enrolled in a study was analyzed. A significant weight gain was observed in the group supplemented with a modular formula, and there was a significant improvement in Karnofsky's functionality among patients who received the glutamine diet compared to those who received the polymeric formula. There was no significant difference in serum albumin levels between the two groups [89]. In conclusion, early administration of a modular dietetic formula containing glutamine trophic dosing for cachectic patients results in better clinical outcomes compared to a standard rehabilitation polymeric formula [90]. Rapid and progressive weight loss precedes the clinical condition of cachexia and indicates a poor prognosis [91]. The treatment of cachectic states has the potential to improve health status and shorten the length of hospital stay. Modular formula consumption is effective in treating mild to moderate malnutrition, but the consumption of a high-protein glutamine-containing formula by cachectic patients has not been evaluated [92]. The early commencement of a high-protein formula with an immuno-nutricional composition and glutamine from the time of hospital admission is a modifiable and affordable strategy which should be put into practice [93]. The analysis shows that the longer the time until the consumption of the specific formula, the fewer days the patient remains admitted to the hospital [94].

Cancer cachexia is common in patients with advanced cancer or advanced by the presence of advanced disease and/or recent chemotherapy and/or radiotherapy [95]. It has negative consequences on quality of life, physical performance, disease treatment, tolerance and compliance [96]. The early administration of a residential formula modular containing additional glutamine trophic may be an opportunity to enhance early recovery in a cachectic hospitalized patient [97]. More studies are urgently needed to accurately determine which cachectic patients are those who improve more with nutritional interventions, at what time point these should be initiated, at what dose, by what route, and of what composition (modular elements and specific ingredients) [98].

A cross-sectional study examined plasma glutamine concentrations in critically ill patients and found that glutamine deficiency occurs in 56% of subjects. Glutamine-containing EN is best absorbed and utilized when administered in low doses, followed by trophic and immunomodulatory doses [99]. Recent results indicate that there is a strong correlation between mass utilization and basal concentration. Treatment of immunomodulatory glutamine increased plasma levels, making it impossible to increase muscle intracellular glutamine simultaneously [100]. Previous studies suggest that a glutamine fortified modular diet has strong potential in preserving endogenous muscle mass in critically ill catabolic patients [101]. However, most studies included a complex mixture of anabolic/anticatabolic agents with or without parenteral nutritional [102]. A prospective, randomized, blinded, pilot clinical trial was designed regarding the addition of glutamine in trophic doses to a simplified standard monomeric diet to facilitate its near-generic clinical application [103].

A trial enrolled 53 adult cachectic and hospitalized patients, stratifying them into two treatment groups. The test formula was a ready-to-use LGD (Leucine, glutamine, vitamin D) enriched modular formula administered early by tube, specifically developed for glutamine trophic dosing. Signal tests and evaluations were made through bioelectrical impedance analysis and the Phase Angle (PhA) diagnostic bioelectrical index [104]. The recovery of muscle mass in patients deemed free from tumoral patients may be considered a positive response, given the prognostic significance in C-reactive protein-correlating tumor evolution [105]. Maintaining or improving PhA is found in numerous forewarning situations and considered in different or innovative physiopathogenic ways [106]. A multicentric randomised phase II dysimmune trial in a de novo metastatic or relieving and asymptomatic node-operated relapse-metastatic context has been initiated [107]. Daily flexible-dose glutamine enriched modular formula administered trophic-dosi early by a nasogastric tube could limit muscle wasting better [108]. A retrospective study has shown a significant level of care-

related side effects, and using a multidisciplinary writing method will be necessary for each patient support for care to ensure they receive best standard care [109]. Areas for future research include assessing the effect of the intervention in a larger and more diverse group, identifying additional effective interventions in treating cachexia, and conducting longitudinal work to extract more insight into the lifelong course of cachexia [110].

5. Conclusion

The research indicated that trophic feeding and enteral arginine supplements enhance gastrointestinal motility. Nevertheless, there were no substantial changes in the rates of morphine administration. Administering nutrition through nasogastric tubing using a specialised formula enriched with glutamine, at a trophic feeding rate of approximately 10-20 ml per hour, is unlikely to disrupt gastrointestinal tolerance or significantly increase residual volume. This approach can have a substantial impact on clinical outcomes and help alleviate the consequences of cachexia, particularly in patients experiencing acute and chronic stress, including those with cancer. Prospective, multisite, randomised, controlled studies with a high sample size are required to ascertain the causative role of glutamine-rich trophic feeding specialised formula in hospitalised hypoalbuminemic cachectic patients.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

There is no conflict of interest in this manuscript

Statement of ethical approval

This project received ethical approval from our Institutional Review Board (IRB) on July 16, 2024. The ultimate endorsement of this study was conducted by the Directorate of Professional Training and Planning at 2 Feb 2025. The permission form was waived in this study due to its retrospective nature, and the study adhered to the protocols and guidelines entirely compliant with the Helsinki standards.

Statement of informed consent

Owing to the retrospective design of this study, the informed consent form was waived.

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