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REVIEW

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Nutritional modifications to ameliorate stress hyperglycemia in critically ill patients: a systematic review

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Abstract

Background and aims Appropriate nutritional support in critical care may favorably influence outcomes by attenuating the detrimental effects of hyperglycemia associated with the critical illness. This systematic review aims to present and evaluate different nutritional interventions to balance risks and rewards for critically ill patients.

Methods In this systematic review, we searched online databases for several variations of terms related to critically ill patients with stress-hyperglycemia (participants), nutrition modalities (intervention), glycemic control (outcomes), and randomized controlled trials (study design) between the inception of the databases and October 2023.

Results The literature search and manual searching provided 2589 articles. After removing the duplicates and excluding studies based on their abstracts or full-text assessment, 37 studies were identified as eligible for inclusion. The heterogeneous nature of these investigations precluded us from pooling data and performing meta-analysis to draw robust conclusions based on statistical analyses. The literature review in this area reveals two general perspectives for achieving this goal: optimizing various aspects of providing macronutrient support and nutritional supplementation.

Conclusions The optimal approach to feeding critically ill patients remains unresolved despite numerous randomized controlled trials. Individual patient characteristics significantly influence optimal nutritional management. However, some general recommendations convey benefits for patients in the intensive care unit (ICU). Early and continuous enteral nutrition is the usual method of providing nutritional support in practice. Hypocaloric feeding and reducing carbohydrate intake are effective methods for managing SIH; however, they should be tailored to each patient's clinical characteristics. Supplementation with certain nutrients shows promise in specific groups, but more research is needed. Overall, personalized approaches based on ongoing research are the best we have now. Future studies will hopefully refine treatments and improve outcomes for these patients.

Keywords Stress hyperglycemia, Nutrition, Critical illness

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Introduction

Critically ill patients experience sudden and complex metabolic and hormonal changes due to the activation of the autonomic stress response [1]. Metabolic changes during critical illness are a part of the body's adaptive mechanism to survive the condition. It involves a complex interplay of neuroendocrine changes, resulting in increased gluconeogenesis, glycogenolysis, and insulin resistance. Stress hyperglycemia, defined as a blood glucose level above 180 mg/dL in patients without pre-existing diabetes, indicates disrupted glucose metabolism and is linked to a higher risk of infectious complications [2], mortality in both intensive and non-intensive care patients, and prolonged hospital stays [3].

Altered glucose metabolism is not the only adverse effect of critical illness on metabolism. The release of stress hormones, inflammatory mediators, and the dysfunction of anabolic hormones during critical illness contribute to a reduced response to sufficient protein intake, leading to a loss of lean body mass and subsequent clinical complications.

Recently, there has been a growing interest in the "food as medicine" concept. One area where this approach may be particularly beneficial is managing blood glucose levels in response to stress. Appropriate nutritional support may promote recovery by alleviating the negative impact of critical illness on nutritional status, such as the accumulation of energy debt and protein breakdown. However, it is not without risks and may exacerbate hyperglycemia commonly seen in critically ill patients.

The prior review article has examined the impact of hypoglycemic agents and anesthetic techniques on mitigating stress-induced hyperglycemia in critically ill patients [4]. Despite numerous research studies investigating strategies to optimize the benefit-to-risk ratio of nutritional support in critically ill patients, a comprehensive systematic review evaluating these studies is lacking. So, this systematic review aims to present nutritional modifications and assess their safety and effectiveness in managing blood sugar levels in critically ill patients. The goal is to advance research in this field and provide insights to guide future clinical practice.

Methods

Literature search

In this systematic review, we searched online databases PubMed, EMBASE, ISI WEB OF SCIENCE, Scopus, Cochrane Central, Google Scholar, and the trial registry clinicaltrial.gov for randomized controlled trials published between the inception of the databases and October 2023.

The search strategy consisted of several variations of terms related to critically ill patients with stress hyperglycemia (participants), nutrition modalities (intervention), glycemic control (outcomes), and randomized controlled trials (study design) with no language restrictions. The keywords used in the literature search were "hyperglycemia OR glucose intolerance OR hyperinsulinism OR glucose metabolism disorders OR insulin resistance OR Glycemic control OR blood glucose control AND Surgical patients OR surgery OR surgical procedure OR operative procedure AND nutrition OR enteral OR parenteral OR feeding AND Critical illness OR critical care OR critically ill OR intensive care AND Randomized controlled trial, Traumatic, medical". The keywords from each part were combined using Boolean operators. Reference lists of the included studies were also manually examined to identify any additional relevant studies.

Eligibility criteria and study selection

We aimed to include all studies that had the following characteristics:

RCTs (study design) conducted to evaluate the effects of nutritional modification (intervention) on at least one measurement of glycemic control in adults (age > 18 years) with stress-induced hyperglycemia (SIH) in critical illness without diabetes (population).

After importing the retrieved studies and removing duplicate records using bibliography management software (EndNote®), two reviewers (F.R. and M.N.) independently screened the titles and abstracts for relevance in the first stage of study selection. They then extracted and selected eligible full-text and abstract-form studies. In the second stage, two investigators independently examined the full texts of the selected studies using a standardized eligibility form that was based on our pre-specified PICO criteria.

Data extraction

We extracted the following data from the included studies: the last name of the first author, year of publication, study location, treatment and follow-up duration, sample size, and our pre-specified PICO information. Other extraction data included mean age, body mass index (BMI), gender of the study population, and baseline glucose levels. We used a standardized data sheet based on the Cochrane Consumers and Communication Review Group's data extraction template.

Risk of bias assessment

We assessed the methodological quality of the included studies using the Cochrane quality assessment tool, which evaluated the following domains: (a) random sequence generation, (b) allocation concealment, (c) blinding of participants and personnel, (d) blinding of outcome assessment, (e) incomplete data outcome, and

(f) selective outcome reporting. Judgment about the risk of bias arising from each domain is determined based on the responses to the signaling questions on a checklist (low risk, high risk, or unclear).

Two investigators independently conducted the screening, data extraction, and risk of bias assessment. Any discrepancies were attempted to be resolved through thorough discussion. A third investigator (Sh.F.) was also considered to adjudicate and resolve any differences.

Results and discussion

The literature search and manual searching provided 2589 articles. After removing the duplicates (958 articles) and excluding studies based on their abstracts or full-text assessment (1568 articles), 37 studies were identified as eligible for inclusion (Fig. 1).

Tables 1 and Supplementary Material 1 represent the characteristics of the studies and participants included in the systematic review and risk of bias assessment, respectively.

The heterogeneous nature of these investigations precluded us from pooling data and performing meta-analysis to draw robust conclusions based on statistical analyses. A comprehensive literature review identified two primary perspectives on nutritional modifications for managing blood sugar levels in critically ill patients. These perspectives, along with corresponding recommendations, are discussed in detail in the following sections.

– Optimize various aspects of providing macronutrient support, including timing, delivery method, and the composition of nutritional formulas.

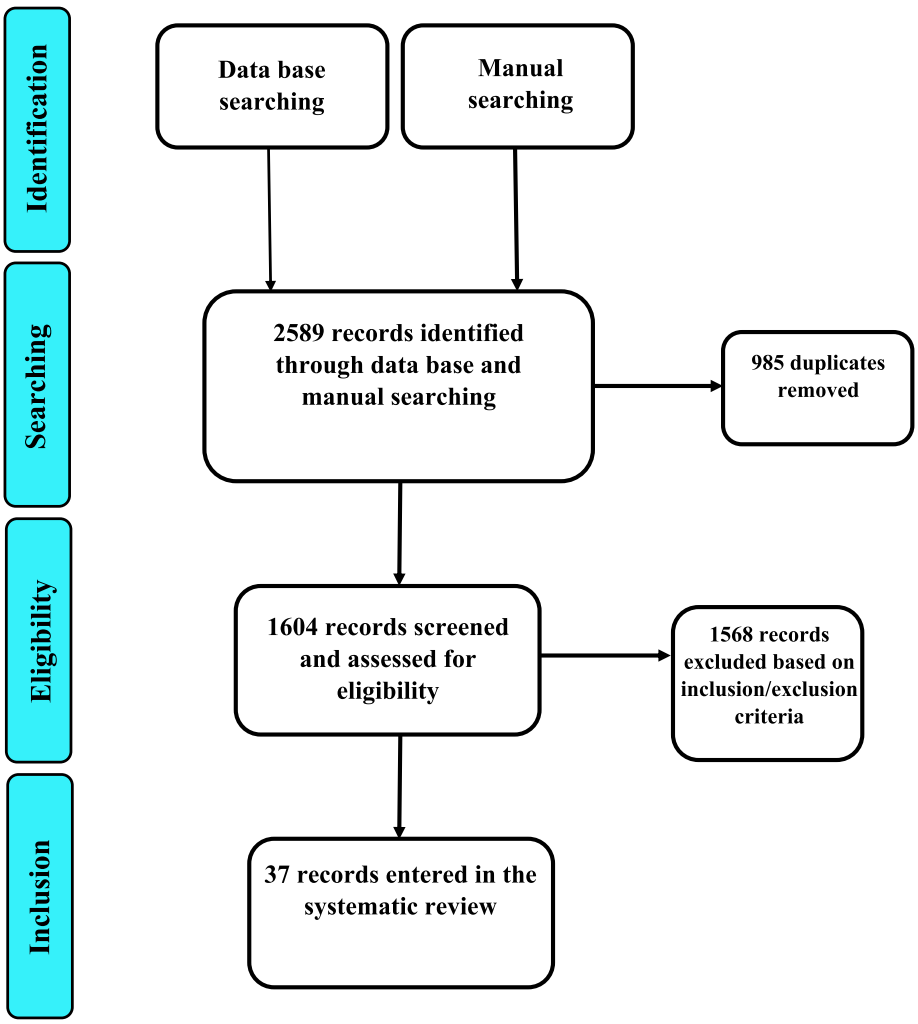

Fig. 1 PRISMA flow diagram

Table 1 Characteristics of the included studies

Nutrition								
Risk of bias	**Baseline glycemia**	**BMI ($kg.m^{-2}$)**	**Male (%)**	**Mean age, years**	**Reported outcomes**	**Study description**	**Study population**	**Authors, year, study design, country**	
1. Timing and mode									
High risk	NA	NA	NA	I: 53.7 ± 15.3 C: 53.9 ± 14.5	Insulin consumption to control the level of glycemia and insulin resistance due to the infection complications were significantly lower in the early nutrition group	Patients were randomized in two groups: Early nutrition group: The nutrition begun within 72 h after ICU admission Late nutrition group: The nutrition begun more than 72 h after ICU admission Study duration: - Follow-up duration: 7 days	Patients with neurosurgical disease and SIRS complications	Pilika et al. 2015, RCT, Albania	1
High risk	NA	SF: 24 CF: 23	58%	SF: 66 CF: 55	There were no significant differences in the average glucose levels and feeding intolerance between the groups. Hypoglycemia was not found in either group. However, hyperglycemia was more common in the CF group	After achieving 80% of the nutrition target calories (25 $kcal{\cdot}kg^{-1}{\cdot}day^{-1}$) through continues gastric tube feeding, patients were randomly assigned into two groups: Sequential feeding (SF) group: The total daily dosage of enteral nutrition was equally distributed to three time periods Continuous feeding (CF) group: Patients in the CF group received CF at a constant rate by an enteral feeding pump Study duration: > 7 days Follow-up duration: 1 month		Ren et al. 2021, RCT, USA	2
High risk	NA	I: 30.5 ± 8.6 C: 30.7 ± 8.1	62%	I: 60.0 ± 20.6 C: 59.2 ± 17.8	The immediate 12-h period after percutaneous endoscopic gastrostomy (PEG) showed significantly lower glycemic variability and median tube feeding (TF) volume for patients in the CTF group. All subsequent time periods (up to 18 days after PEG) showed no differences in glycemic variability, insulin usage, tube feeding volume, or caloric intake. Insulin use increased for both groups when comparing the first 24-h post-PEG values to measurements from day 8. There were no differences in tube feeding interruptions, time to achieve ≥ 80% of the nutritional delivery goal, or hypoglycemic episodes	Patients undergoing percutaneous endoscopic gastrostomy (PEG) placement for EN were randomly assigned to: Intervention group: continuous tube feeding (CTF) Control group: bolus tube feeding (BTF) Study duration: 18 days Follow-up duration: -	Surgical and neurologic critical care units	Evans et al. 2016, RCT, USA	3
High risk	I: 139.98 ± 21.59 C: 140.25 ± 23.31	NA	76%	I: 41.4 ± 15.3 C: 41.1 ± 12.4	Patients who received continuous feeding showed significantly better blood glucose control, as measured by their blood glucose levels	Intervention group: Patients were fed continuously using a pump syringe for 24 h. The gavage volume was increased by 20–50 cc every 4–6 h to reach the calculated calorie and volume requirements for the patient Control group: The required calories were divided into six portions and administered via syringe over 10–20 min. The volume of each portion was increased by 50 cc based on the patients' tolerance and the residual volume of their stomach (< 150 cc) every 6 h, in order to reach the targeted volume and calorie intake Study duration: 4 days Follow-up duration: -	Mixed ICU	Shahriari et al. 2015, RCT, Iran	4

Table 1 (Continued)

Nutrition									
Some concern	NA	NA	81%	I: 55.2 (51.0–59.3) C: 60.3 (56.0–64.1	Glycemic variability, defined as the coefficient of variation for glucose concentrations, was higher with intermittent feed. However, days with reported hypoglycemia and insulin usage were similar in both groups	Intervention group: Intermittent enteral feeding from six 4-h feeds per 24 h Control group: Standard continuous enteral feeding Study duration: 10 days Follow-up duration: 10 days	Mechanical-ventilated patients with multiorgan failure	McNelly et al. 2020, RCT, Britain	5
High risk	NA	NA	100%	I: 40.7 ± 10.1 C: 40.2 ± 6.8	There was no significant difference in the blood sugar levels, respiratory quotient (RQ), and resting energy expenditure (REE) between the groups	Intervention group: Patients received six bolus feeds (30 kcal/kg/day) every 3 h for 18 h, with a 6-h rest at night Control group: Patients received feeds (30 kcal/kg/day) for 18 h per day, with a 6-h rest at night Study duration: 1 day Follow-up duration: -	Neurosurgical patients requiring mechanical ventilation	Maurya et al. 2011, RCT, India	6
High risk	I: 126.12–144.14 C: 144.14–162.16	NA	64%	I: 54.93 ± 20.96 C: 52.14 ± 13.77	There were no statistical differences in blood glucose and C-peptide levels, number of patients experiencing stress hyperglycemia, number of patients experiencing stress hypoglycemia or glycemic variability between the groups	If there were no absolute contraindications, EN was initiated within 48 to 72 h of admission to the ICU Intermittent feeding group (IF group): The intermittent protocol involved initial feeds of 100 to 300 mL every 4 to 8 h. This was repeated twice and, if tolerated, they were advanced by 100 to 300 mL every 1 to 2 days to the volume goal. Each intermittent feeding was delivered via an enteral feeding pump during a 30- to 60-min period of time Intermittent semi-solid feeding group (IS group): The IS only increased the semi-solid agent before the EN application within 1 h, which is low methoxy pectin gel and water-soluble dietary fiber form apple and citrus peel by binding to calcium ions in EN to increase the viscosity, but do not change any chemical properties of EN Study duration: 3 days Follow-up duration: 30 days	Critical patients with brain or spinal cord injury	Lu et al. 2018, RCT, China	7
2. Macronutrient composition									
High risk	NA	NA	NA	NA NA	Blood glucose, Insulin activity, glucose utilization	Both the study and the control parenteral formulas were isocaloric (carbohydrates: 0.25 g/kg body weight/h; lipids: 0.166 g/kg body weight/h) and isonitrogenous (amino acids: 0.0625 g/kg body weight/h) with different compositions: Intervention group: glucose solution + lipid emulsion Control group: fructose solution + lipid emulsion Study duration: 10 h Follow-up duration: -		Adolph et al. 1992, RCT, Germany	8

Table 1 (Continued)

Nutrition									
High risk	NA	NA	65.8	45.4	The levels of blood glucose and insulin needs were significantly lower than those of the control group	Patients in the intervention group received a formula lower in carbohydrate and higher in fiber Study duration: 14 days	Critical patients with trauma or sepsis	Celaya et al. 1992	9
High risk	I: 226.1 ± 73.87 C: 213.8 ± 67.83	I: 24.7 ± 2.57 C: 25.7 ± 2.41	82%	I: 64.2 ± 14.95 C: 64.6 ± 9.63	Patients in the intervention group exhibited lower plasma glucose levels and decreased use of insulin	Both the study and the control formulas were isocaloric but with different caloric distribution (%Protein/%Carbohydrate/%Fat): Intervention group formula: 20/40/40 Control group formula: 22/49/29 Intervention formula also had higher fiber and MUFAs contents Study duration: 14 days Follow-up duration: 14 days	Medical ICU patients	Mesejo et al. 2003, RCT, Spain	10
	I: 103.5 (86–128.5) C: 108.5 (92.5–116)	NA	77.5%	I: 43.5 ± 17.2 C: 53.1 ± 17.9	The low-calorie parenteral nutrition (PN) formula led to a reduction in both the frequency and severity of hyperglycemia, defined as a blood glucose level ≥ 200 mg/dL, as well as decreased insulin needs	Intervention group: Nutritional goals in the intervention group were a hypocaloric PN of 20 nonprotein kilocalories per kg per day Control group: Control group goals received a normocaloric PN of 30 nonprotein kilocalories per kg per day The calorie content from lipids was set at 1000 kcal three times a week for all patients, so the calorie intake only differed based on the amount of carbohydrates given. Protein needs were adjusted according to estimated metabolic stress for each individual Study duration: - Follow-up duration: -	Consecutive surgical patients	Ahrens et al. 2005, RCT,	11
High risk	NA	27.1 ± 4.9	82%	38.1 ± 17.5	Patients in the L group had significantly lower blood glucose levels. The number of patients requiring insulin and the amount of insulin used were also lower in the L group. However, these two indices were not statistically significant	Continues parenteral nutrition started on study day 1. Both groups received 20% of their parenteral energy supply as amino acids, but with different lipid/glucose ratios: Intervention group (L group): 75 (olive oil emulsion)/25 Control group (G group): 37 (soy bean emulsion)/63 Enteral nutrition started on day 1 with a daily maximum of 5 kcal/kg during the first 6 days. The L group also received an enteral diet containing high fat based on olive oil (lipid/glucose 60/40; the G group received an enteral standard diet (lipid/glucose 44/56). After day 6, the parenteral energy supply was reduced while the enteral energy was increased dependent on the patients' gastrointestinal tolerability The cumulative daily total mean energy intake was significantly lower in the L group Study duration: 14 days Follow-up duration: 6 months	Patients with trauma, and requiring mechanical ventilation	Huschak et al. 2005, RCT, Germany	12

Table 1 (Continued)

Nutrition									
High risk	NA	I: 64.2 ± 14.95 C: 64.6 ± 9.63	54%	I: 56.2 ± 4.9 C: 56.3 ± 5 0/24 (0%)	Plasma glucose, insulin, cortisol, and glucagone levels were slightly but not statistically significant, lower in the intervention group	TPN was started within 1–4 days of admission to the ICU TPN provided 1.5 g protein/kg/day, 0.25 g/kg/day lipids and the remaining 62% of the total energy as dextrose. Comparison groups were different in lipid emulsion type: Intervention group formula: n-3 PUFA enriched lipid emulsion Control group formula: Standard soy bean emulsion Study duration: 5 days Follow-up duration: 5 days	Surgical ICU patients	Tappy et al. 2006, RCT, Switzerland	13
High risk	130	22.6	NA	64 0%	Mean blood glucose and maximum blood glucose levels during the feeding and the study periods were significantly lower in the intervention group. Patients who received the study formula also experienced lower incidance of hyperglycemia and glycemic variability	Both the study and the control formulas were isocaloric but with different caloric distribution %(Protein/Carbohydrate/Fat) and carbohydrate type (different glycemic index): Intervention group: 20/50.3/29.7 Composition of carbohydrate: Dextrin, 22.8% Isomaltose, 68.3% Other, 8.9% Control group: 16/58.8/25.2 Composition of carbohydrate: Dextrin, 40% Glucose, 20% Fructose, 21% Other, 19% Study duration: 1 day Follow-up duration: 10 days	Surgical ICU patients	Egi et al. 2010, Cross-over study, Japan	14
High risk	NA	NA	54%	I: 56.1 ± 20.4 C: 56.4 ± 21 14/351 4%	Median blood glucose levels were significantly lower in the control group. However, the incidence of hypoglycemia and insulin consumption were significantly lower in the intervention group. Median length of insulin usage in the subgroup of patients remained in the ICU more than 5 days was slightly, but not statistically significant, shorter in the control group	Patients were on different glycemic control protocols and received different enteral formulas: Intervention group (CRS): Patients received intravenous hydration with a glucose-free solution (Ringer III) and enteral nutritional formula containing 33.3% carbohydrates, 16.7% proteins, and 50% lipids. These patients received regular insulin subcutaneously four times daily, aiming to maintain blood glucose levels less than 180 mg/dL, and in stable patients, ideally less than 150 mg/dL Control group (IIT): Continuous intravenous insulin infusion was adjusted to maintain glycemic levels less than 150 mg/dL and in stable patients, ideally between 80 and 120 mg/dL. Patients were submitted to capillary glycemic measurements every 2 h. The insulin dose was adjusted according to an algorithm run by nurses and overseen by physicians. These patients received glucosaline (5% glucose + 0.9 NaCl) hydration and enteral nutrition with a formula containing 45% carbohydrates, 17% proteins, and 38% lipids The two groups did not differ in the percentage of nutritional requirements they received Study duration: 14 days Follow-up duration: -	Multidisciplinary ICU of a general hospital and to an 11-bed trauma center ICU	de Azevedo et al. 2010, RCT, Brazil	15

Table 1 (Continued)

Nutrition									
High risk	150.5 ± 51	26	75.8%	58.3 0%	Both diabetes-specific formulas reduced insulin requirements, improved glycemic control, and lowered the risk of acquired infections compared to the standard formula. Compared to the control-specific formula, the new-generation formula also improved capillary blood glucose levels	The study and control formulas had different caloric distribution %(Protein/Carbohydrate/Fat): Group A: New-generation diabetes-specific formula (study diet) 23/33/40 Group B: Standard formula 20/44/34 Group C: Control diabetes-specific formula 20/30/49 The two specific formulas contained greater proportions of MUFA and the study diet also had higher ω-3, EPA, and DHA contents. All the patients received similar caloric and nitrogenous support Study duration: 28 days Follow-up duration: 6 months	Critically ill patients on mechanical ventilation	Mesejo et al. 2015, RCT, Spain	16
High risk	NA	25	50%	I: 53.8 ± 19 C: 51.8 ± 20.3	Patients in the hypocaloric group exhibited lower average daily insulin requirements and a lower percentage of patients requiring any insulin	Ideal body weight was used to calculate caloric and protein requirements Intervention group: Nutritional goals in the intervention group were a hypocaloric EN of 15 kcal/kg per day of total calories and high protein intake (1.7 g of protein/kg per day) Control group: Control group goals were a normocaloric EN of 25 kcal/kg per day with high protein intake (1.7 g of protein/kg per day) All patients received allocated nutritional regimen until day 7. If further EN was necessary, all patients received normocaloric nutrition Study duration: 28 days Follow-up duration: 28 days	Critical patients with organ failure	Rugeles et al. 2016, Colombia	17
High risk	NA	I:28.6 ± 6.5 C:27.1 ± 6.8	66%	I: 67.6 ± 11.5 C: 64.3 ± 11.5	Rate of nosocomial infections during the ICU stay Insulin demand, ICU, hospital, and 28-day all-cause mortality rates	Intervention group: normocaloric group (receiving the total daily energy expenditure) Control group: hypocaloric group (receiving 50% of the daily energy expenditure) Total daily energy expenditure is measured with an indirect calorimeter. If this was not possible, the Ireton-Jones prediction equation was used Study duration: 7 days Follow-up duration: 28 days	Medical ICU patients	Petros et al. 2014, RCT, Germany	18
-	I: Group B: 127.25 ± 37.94 Group C: 129.06 ± 31.35 C: 113.96 ± 28.28	NA	I: 62.5% C: 87.5%	I: Group B: 58.50 ± 22.25 Group C: 5.56 ± 23.96 C: 56.81 ± 24.17 45/93 (48.38%)	Glycemic control and lipid profile, occurrence of organ failure and length of stay mortality in ICU. Mortality, SOFA score	Intervention (fat bases diet): Group B: (Protein/Carbohydrate/Fat) %: 20/35/45 including half of olive oil and half sunflower oil Group C: (Protein/Carbohydrate/Fat) %: 20/35/45 sunflower oil Comparison: (Protein/Carbohydrate/Fat) %: 20/50/30 Study duration: 14 days Follow-up duration: -		Nourmohammadi et.al. 2017, RCT, Iran	19

Table 1 (Continued)

Nutrition									
High risk	139 ± 20.4	I: 26.2 ± 5.2 C: 27.5 ± 4.4	46.6%	I: 60 ± 12 C: 58 ± 16 16/60 (26.7%)	Measures of blood glucose levels, glucose AUC, and glycemic control status were not statistically different between the groups	Both the study and the control formulas were isocaloric but with different caloric distribution %(Protein/Carbohydrate/Fat): Fat-based formula (Group A): 18/37/45 and 2.3 g fiber Glucose-based formula (Group B): 15/55/30 and 1.5 g fiber Study duration: 7 days Follow-up duration: 7 days	Medical ICU patinets on mechanical ventilation	Wewalka et al. 2018, Austria	20
High risk	147 ± 39.6	I: 26.7 ± 4.8 C: 28.5 ± 5.2	56.4%	I: 66.1 ± 13.2 C: 67.1 ± 10	LCF showed a trend toward a modest reduction in mean glucose and significantly lower insulin requirements compared with standard feeding, but had no effect on glucose variability or time spent in the target range	Both the study and the control formulas were isocaloric but with different caloric distribution %(Protein/Carbohydrate/Fat): Intervention (LCF) group: 22/33/45 Comparison: Isocaloric standard enteral formula Study duration: 3 days **Follow-up duration:** -		van Steen et al. 2018, RCT, Netherlands	21
High risk	224.9 ± 37.7	NA	50%	I: 61 C: 62	Measures of mean blood glucose levels and insulin requirements were not significantly different between the groups	Both the study and the control formulas were isocaloric but with different caloric distribution %(Protein/Carbohydrate/Fat): Intervention group: 20/35/45 Control group: 20/50/30 Study duration: 15 days Follow-up duration: -	Mixed ICU	Vahabzadeh et al. 2018, RCT, Iran	22
Some concern	> 180	I: 28.67 ± 4.74 C: 29.53 ± 7.92	58.5%	I: 62.4 ± 9.9 C: 62.2 ± 11.3	The intervention group had a lower mean blood glucose level and a lower probability of blood glucose levels outside the target range Glycemic variability and insulin usage were also lower in the intervention group	Intervention group: 20/35/45 1.25 kcal/ml Control group: 20/44/34 1 kcal/ml There was a small difference in the mean percentage of energy requirements met (intervention group: 72.9 vs. control: 79.1, $p = 0.04$) or protein delivered (intervention group: 78.2 vs. control: 85.4, $p = 0.03$) Study duration: 2 days Follow-up duration**:** 28 days		Doola et al. 2019, RCT, Australia	23
High risk	< 180	I: 33.4 ± 4.6 C: 33 ± 5.8	51.5%	I: 61 ± 14.6 C: 63.3 ± 11.9	Blood glucose, mean rate of hyperglycemic (> 150 mg/dl) events, mean rate of glycemic events between 80–110 mg/dl, number of glucose events < 80 mg/dl and < 60 mg/dl, number of insulin administration, average daily doses of insulin	Both the study and the control formulas were isocaloric but with different caloric distribution %(Protein/Carbohydrate/Fat): Intervention group: 37/29/34 Control group: 25/45/30 Because of the difference in non-protein calories between the groups and considering that their nutrition protocol aimed at achieving the same amount of protein, the experimental group received lower calories; conforming a hypocaloric regimen Study duration: 7 days Follow-up duration: 7 days	Critically ill overweight patients on mechanical ventilation	Rice et al. 2019, RCT, USA/Canada	24

Table 1 (Continued)

Nutrition									
Some concern	I: 227 ± 104 C: 194 ± 72	NA	60%	77 ± 9.8 0%	Diabetes-specific enteral formula containing fructose was associated with lower glycemic variability in critically ill patients compared to diabetes-specific enteral formula without fructose	Both enteral formulas were isocaloric. No wash-out period was used once patients were under intensive insulin therapy; the patients received both diets sequentially to avoid hypoglycemic events. At the end of the study, patients followed the usual hospital practice according to the internal routing protocol Intervention group: the nutritional compositions (per 100 mL) of formula with fructose was 100 kcal of energy, 17% of total energy from protein, 48% of total energy from fat and 35% of total energy from carbohydrates (5.34 g of maltodextrin, 1.8 0 g of fructose, and 1.73 g of soy polysaccharides), with 1.40 g of total fiber Control group: the formula without fructose (maltodextrin-based) composition (per 100 mL) was 100 kcal of energy, 22% of total energy from protein, 42% of total energy from fat, and 36% of total energy from carbohydrates (maltodextrin) with 1.20 g of total fiber Study duration: 2 days Follow-up duration: 4 days		Kumbier et al. 2021, Crossover study, Brazil	25
3. Supplementation									
High risk	I: 152.61 ± 21.02 C: 153.30 ± 21.17	NA	69%	I: 42.8 C: 44.37 0%	Measures of blood glucose levels were not different between the groups on day 1; however, patients in the intervention group had significantly lower blood glucose levels on day 3. Administration of vitamin D plus calcium also reduced the undesirable event rate defined as blood glucose levels exceeding 100 mg/dL by 47%	Intervention group: Patients in the intervention group received 1000 IU vitamin D plus 1000 mg calcium every day, for a period of 72 h Control group: - Study duration: 10 days Follow-up duration: -	Critical non-diabetic patients	R.P.E.a.A.H.AA et al. 2015, Spain	26
High risk	I: 152.61 ± 21.02 C: 153.30 ± 21.17	NA	69%	I: 42.8 C: 44.37	1000 international units of vitamin D plus 1000 mg of calcium reduced blood glucose concentration and undesirable events, such as hypoglycemia, defined as blood glucose levels below 100 mg/dL after 72 h	Intervention group: 1000 IU vitamin D plus 1000 mg calcium every day, for a period of 72 h Control group: - Study duration: 3 days Follow-up duration: -		Páez et al. 2015, RCT, Colombia	27
High risk	I: 147 ± 17.04 C: 142.67 ± 24.44	I: 25.53 ± 4.51 C: 26.55 ± 5.54	52%	I: 54.73 ± 17.56 C: 52 ± 17.69 9/59 (15.3%)	Improvement in fasting plasma glucose levels was observed on day 7 of the study compared to the baseline status in both the vitamin D and placebo groups Fasting plasma insulin levels did not change significantly during the study period in both groups Fasting plasma adiponectin levels increased significantly in the vitamin D group, but not in the placebo group The HOMA-IR, as an index of insulin resistance, exhibited a decreasing trend in the vitamin D group, but the difference was not statistically significant. However, no change in HOMA-IR was observed in the placebo group Changes in the HOMA-AD index, as another index, were not significant in the both groups	Intervention group: Patients in the intervention group received a single dose of 600,000 IU vitamin D3 as intramuscular injection at time of recruitment Control group: Patients in the control group received placebo Considering 25(OH) D concentration < 30 ng/ml as a cut-off for vitamin D deficiency, all and 95% of patients in vitamin D and placebo groups, respectively, had vitamin D deficiency at the time of admission to the ICU Study duration: 7 days Follow-up duration: 7 days		Alizadeh, et al. 2016, RCT, Iran	28

Table 1 (Continued)

Nutrition									
High risk	> 180	NA	%60	I: 59.16 ± 17.77 C: 51.93 ± 12.26	At Day 3, significant differences were observed between the Mg group and the placebo group in the mean changes from baseline in blood sugar and insulin resistance indices	Intervention group: patients in the Mg group received a single-loading dose of Mg (7.5 g of Mg in 500 mL normal saline as intravenous infusion over an 8-h period) at the time of recruitment Control group: The placebo group received the same amount of normal saline Study duration: 8 h Follow-up duration: 3 days	non-diabetic critically ill patients	Heidary et al. 2018, RCT, Iran	29
High risk	NA	I: 24.46 C: 24.18	77%	I: 34 C: 36 0%	AUC for blood glucose levels, number of patients requiring insulin, and insulin consumption were lower in the inter-evention group	Their protocol involved providing 30% of the total caloric and protein intake on the first day, 60% on the second day, and 25 kcal/kg/day on the third day. Nutritional support was begun within 24 h via both parenteral and enteral routes Intervention group: Glutamine supplementation (0.5 g/kg/day) began alongside nutritional support for at least 7 days Control group: Standard nutrition Study duration: 7 > days Follow-up duration:	Polytrauma patients	Grintescu et al. 2015, RCT, Romania	30
Some concern	NA	I: 24.5 ± 4.3 C: 25.5 ± 3.7	74%	I: 51 ± 17.9 C: 54.7 ± 18.9 10/114 (8.8%)	Hyperglycemia (defined as blood glucose level > 10 mmol/l), and the number of patients requiring insulin were significantly lower in the intervention group	Both groups of patients received isonitrogenous (0.35 g N·kg^{-1}·day^{-1}) and isocaloric (37 kcal·kg^{-1}·day^{-1}) regimens. Supplied as constant intravenous infusion over 24 h via central veins as follows: 1.5 g·kg^{-1}·day^{-1} of amino acids, 6 g·kg^{-1}·day^{-1} of glucose, 1.5 g·kg^{-1}·day^{-1} of lipid emulsion, and Intervention group: 0.5 g·kg^{-1}·day^{-1} of Ala-Gln dipeptide or Intervention group: 0.7 g·kg^{-1}·day^{-1} of Ala -Pro Standard vitamins, trace elements, and electrolytes were supplied according to the usual practice of each hospital Study duration: 5–10 days Follow-up duration: 6 months	Mixed ICU patients	Dechelotte et al. 2006, RCT, France	31
High risk	NA	I: 24.8 ± 3.1 C: 25.3 ± 2.8	62.5%	I: 30 ± 13 C: 32 ± 15 9/49 18.4%	Measurements of glycemic control were reported on day 4 and day 8 On days 4 and 8, insulin-mediated glucose disposal was significantly higher in patients who received AG. Parenteral supplementation of alanyl-glutamine dipeptide was associated with better insulin sensitivity	Parenteral nutrition was started 24 h. after admission When intramucosal pH measured by gastric tonometry was > 7.32, enteral feeding was started with a nutritionally complete oligopeptide-based diet not containing Ala-Gln (AG) dipeptides. Maximal daily dose of enteral nutrition was adjusted so that the energy intake contributed by the enteral feed was never more than half of the patient's measured energy expenditure. All patients were receiving isocaloric nutrition Intervention group: 1.1 g·kg^{-1}·24 h^{-1} amino acids and 0.4 g·kg^{-1}·24 h^{-1} of Ala-Gln supplementation by parenteral or enteral route Comparison: 1.5 g·kg^{-1}·24 h^{-1} amino acid without Ala-Gln by parenteral or enteral route Study duration: 8 days Follow-up duration: -	Multiple-trauma patients admitted to ICU	Bakalar et al. 2006, RCT, Czech Republic	32

Table 1 (Continued)

Nutrition									
High risk	NA	NA	64.5%	I: 68 C: 65 15/132 11.4%	Mean blood glucose levels and mean insulin requirements were significantly lower in the intervention group. Multivariate analysis also showed a 54% reduction of the amount of insulin for the same levels of glycemia in the intervention group	All the patients received an isocaloric and isonitrogenous total parenteral nutrition. Nutritional needs were calculated: 0.25 gr/kg/day nitrogen and 25 kcal/kg/day: Intervention group: 0.5 g/kg/day glutamine dipeptide Control group: The same amount of amino acids Study duration: 5–9 days Follow-up duration: 6 months		Grau et al. 2011, RCT, Spain	33
High risk	NA	I: 21.41 ± 3.23 C: 22.19 ± 3.54	77%	I: 72.11 ± 10.62 C: 74.93 ± 10.44	Patients in the intervention group had lower incidence of hyperglycemia and gastric retention. MHLJDD also shortened the mechanical ventilation dependency and ICU stay of septic patients. However, the difference in 60-day mortality rate between the two groups was not statistically significant	Patients were randomly assigned to receive: Intervention group: the standard EN nutrition supplemented with a Chinese traditional remedy (HuangLian JieDu) Control group: Standard EN Study duration: 60 days Follow-up duration: 60 days	Septic patients	Wang et al. 2022, RCT, China	34
Some concern	NA	NA	NA	NA	ALA supplementation significantly reduced blood glucose levels and improved insulin resistance and antioxidant capacity in critically ill patients	Intervention group: Patients in the intervention group received 900 mg of α-Lipoic Acid (ALA) every day Control group: Patients in the intervention group received 900 placebo every day Study duration: 10 days Follow-up duration: 28 days		Hejazi et al. 2018, RCT, Iran	35
High risk	I: 164.13 ± 17.80 C: 162.10 ± 11.17	NA	52%	I: 54.37 ± 19.18 C: 59.53 ± 17.37	There was a significant reduction in mean fasting blood sugar (FBS) levels of both groups. However, the reduction in the mean FBS level in the control group was greater than that of the intervention group There was a significant reduction in mean postprandial blood sugar (PPBS) levels of both groups. However, the reduction in PPBS levels of the intervention group was greater than that of the control group	Intervention group: 3 g of fenugreek seed powder by gavage, twice a day Control group: routine care (insulin injections via an infusion pump) Study duration: 10 days Follow-up duration: -		Kooshki et al. 2018, RCT, Iran	36
Some concern	I: 129.25 ± 21.75 C: 114 ± 21.45	41.46% were > 25	64.6%	64.1 ± 15.48	L-carnitine supplementation improved insulin resistance, as assessed by HOMA-IR, as well as decreased insulin concentrations and levels of C-reactive protein	Intervention group: Daily oral intake of 1.5 g L-carnitine (LC) Control group: Daily oral intake of 1.5 g placebo Study duration: 7 days Follow-up duration: 28 days		Nejati et al. 2021, RCT, Iran	37

NA not available, *ALA* α-lipoic acid, *BMI* body mass index, *CRS* carbohydrate-restrictive strategy, *DM* diabetes mellitus, *DSFs* diabetes-specific formulas, *ESPEN* the European Society for Clinical Nutrition and Metabolism, *HOMA-IR* Homeostatic Model Assessment for Insulin Resistance, *HOMA-AD* Homeostatic Model Assessment-Adiponectin, *ICU* intensive care unit, *IIT* intensive insulin therapy, *LE* lipid emulsion, *MUFA* monounsaturated fatty acids, *RCT* randomized controlled trial, *SF* sequential feeding, *SOFA* Sequential Organ Function Assessment, *SIH* stress-induced hyperglycemia, *STDF* standard formulas, *TPN* total parenteral nutrition

– Optimize various aspects of providing macronutrient support, including timing, delivery method, and the composition of nutritional formulas.

Optimize various aspects of providing macronutrient support

Insights into the timing and route of administration

Although there is no consensus on the tolerable level of starvation in critically ill patients without harmful consequences, these recommendations are available based on guideline evidence [5]:

- Initiate nutrition as soon as possible, preferably within 24–48 h of the onset of critical illness.
- Enteral nutrition is the preferred method for providing nutritional support to critically ill patients.
- Total or supplemental parenteral nutrition should be considered if enteral nutrition is contraindicated or the nutrition target is not met.
- Evidence suggests that patients receiving parenteral nutrition had significantly higher blood glucose levels than those receiving enteral nutrition [6].

Pilika et al. [7] conducted a randomized controlled trial (RCT) to examine the impact of enteral nutrition timing on insulin resistance in neurosurgical patients. The authors reported that the number of patients who developed insulin resistance and the amount of insulin administered to control glycemia were significantly higher in the late nutrition group. They suggested that initiating nutrition within 72 h in the neurosurgical ICU (intensive care unit) would be preferable.

Insights into the feeding methodology

Intermittent (administering a bolus volume of nutrients at specific intervals) and continuous enteral feeding are two standard modes used to provide nutrition to critically ill patients. The current recommendation in this field for improved control of SIH is:

- Enteral nutrition should be administered continuously in the ICU [8, 9].

Most studies have demonstrated that continuous feeding is comparable or superior to sequential feeding (SF) in managing glycemic control in ICU patients' stress-induced hyperglycemia (SIH) [10–13]. However, Ren et al.'s study [14] showed that the average blood glucose level in the SF method (three times daily) was not inferior to continuous feeding and led to a lower occurrence of hyperglycemia.

More high-quality randomized controlled clinical trials and meta-analyses are needed to evaluate each method's other long-term consequences, such as long-term hyperglycemia, insulin resistance, and skeletal muscle autophagy [9, 15–17].

Insights into the nutrition composition

Multiple research studies have concentrated on various enteral formulas to assess their impact on glycemic control and revealed:

- Hypocaloric nutrition (30–65% of the calculated calory requirement) has been shown to benefit glycemic control in ICU patients compared to the full-calorie feeding group (which had a goal of 90–100% of the calculated requirement) when patients receive the same protein content [18–23].
- Reducing carbohydrate intake (8.5% to 30%) is significantly associated with improved glycemic control and reduced insulin requirements in critically ill patients. This association had a greater effect size in trials involving patients with diabetes mellitus (DM) [19, 24–30].
- The ideal lipid emulsion (LE) combination has not been conclusively determined. However, plasma glucose and insulin levels were lower in the n-3 fatty acid-enriched than soybean lipid emulsion in the conducted study [31].
- A few studies evaluated the metabolic effects of different carbohydrate types in enteral or parenteral nutrition in the ICU. No significant differences in glycemic variability were observed between diabetes-specific enteral formulas with or without fructose [32]. However, the enteral isomaltose group exhibited superior metabolic effects compared to the control group [33]. Additionally, parenteral nutrition utilizing a glucose solution demonstrated better metabolic outcomes than a fructose solution [34].

Hypocaloric nutrition

Hypocaloric nutrition is a strategy that intentionally restricts energy intake and reduces insulin demand while ensuring that protein or fat macronutrients still meet metabolic needs. Although hypocaloric nutrition has been associated with some metabolic benefits, such as lower and less severe episodes of hyperglycemia or decreased insulin consumption in critically ill patients. However, most studies addressing this concept have shown no significant impact on clinical outcomes [18–23] (Table 1).

These beneficial metabolic events were also reported in high-protein, hypocaloric nutrition. Rice et al. [19] conducted a multicenter trial to assess the impact of this

approach on critically ill overweight and obese patients. They examined an experimental enteral nutrition formula with a very high protein content (37%) and low carbohydrate content (29%), compared to a control formula with a high protein content (25%) and standard carbohydrate content (45%). Protein delivery was consistent across all groups during the study period, but energy delivery was significantly lower in the experimental group. They showed a decrease in average blood glucose levels and the frequency of insulin administration in the high-protein, hypocaloric nutrition group.

Petros et al. demonstrated that hypocaloric feeding (11.3 ± 3.1 kcal/kg/day) in the first 7 days in critically ill patients resulted in lower insulin demand and reduced gastrointestinal intolerance. Still, it was associated with more nosocomial infections than normocaloric feeding (19.7 ± 5.7 kcal/kg/day) [21]. The higher rate of nosocomial infections may be attributed to the lower protein intake in these patients.

Reducing carbohydrate intake

The provision of exogenous carbohydrates is associated with increased insulin utilization and glucose variability [29]. Therefore, manipulating carbohydrate intake, particularly by reducing carbohydrate provision in enteral or parenteral nutrition, is one of the most extensively studied strategies for achieving improved glycemic control.

Diabetes-specific formulas (DSFs), in general, have a low total carbohydrate content (35–40% of total calories) and a high-fat content (40–50% of total calories), especially in the form of monounsaturated fatty acids (MUFAs), when compared to standard polymeric formulas. They also feature a variety of carbohydrate sources and are recommended for use in patients with persistent hyperglycemia.

In 2003, Mesejo et al. [30] conducted a multicenter randomized trial to investigate whether a DSF formula would improve glucose control in critically ill hyperglycemic patients. The results revealed a significant improvement in glycemic control and a reduction in insulin requirements among the patients who consumed the low-carbohydrate formula. After the publication of this study, several other studies also revealed the beneficial metabolic effects of various low-carbohydrate enteral formulas with different nutrient compositions [19, 24–29]. Furthermore, the carbohydrate-restrictive strategy (CRS) has been reported to be as effective as intensive insulin therapy (IIT) but with a reduced risk of hypoglycemia [35].

Among the studies examining the effectiveness of CRS, two studies by van Steen and Wewalka [27, 36] did not demonstrate a significant positive impact on glucose regulation in the low-carbohydrate group. Various protocols for providing nutrition and monitoring glucose had an effect on these results.

To reach a definitive conclusion about the effectiveness of the CRS strategy, Eckert et al. [37] conducted a meta-analysis and proposed that reducing carbohydrate intake is significantly associated with improved glycemic control and reduced insulin requirements in critically ill patients. This association had a greater effect size in trials involving patients with diabetes. Patients with diabetes may benefit more from this strategy than non-diabetic patients. One potential explanation is that diabetic patients may experience lower levels of stress hyperglycemia, and low-intensity strategies such as reducing carbohydrate intake may be more beneficial for them compared to non-diabetic individuals.

In addition, another meta-analysis was conducted incorporating findings from 18 randomized controlled trials, comparing the metabolic effects of DSF high in MUFA with standard formulas (STDF) [38]. This analysis focused on adult patients diagnosed with type 1 diabetes, type 2 diabetes, or SIH. The results of this meta-analysis provided evidence that a DSF, comprising oral supplements and tube feeds enriched with MUFAs, yielded improvements in glucose control and metabolic risk factors compared to the STDF in patients diagnosed with diabetes or SIH. The heterogeneity observed in the study population, consisting of patients with DM and those experiencing SIH without diabetes, renders the conclusion inconclusive, specifically for individuals just with SIH.

Despite the potential of DSF to improve glycemic control and insulin requirements, the recently published studies have not demonstrated any superior clinical outcomes, such as ICU length of stay, mechanical ventilation, and mortality, compared to control groups. The extent of carbohydrate reduction is another factor that may affect the metabolic and clinical outcomes of DSF. This is because low-carbohydrate formulas often contain higher fat content than standard formulas, and a high fat content may lead to insulin resistance. The percentage of carbohydrate reduction varied significantly among the studies, ranging from 8.5 to 30%. Hence, determining the optimal amount of carbohydrates is another issue that requires further investigation.

Ideal lipid emulsion

The ideal LE combination should be tailored to the patient's condition, the critical illness' severity, and overall nutritional needs. For example, it has been suggested that n-3 fatty acids modulate inflammatory responses [39, 40], which may decrease insulin resistance. Tappy

et al. [31] conducted a trial in surgical intensive care patients who received total parenteral nutrition (TPN) using either an n-3 fatty acid-enriched or soybean lipid emulsion. Plasma glucose and insulin levels were lower in the TPN-n-3 group, but the difference did not reach statistical significance. Additionally, the energy expenditure was significantly lower in the TPN-n-3 group.

Various carbohydrate types in critical illness

Modifications in the nutritional composition aimed at reducing or preventing stress hyperglycemia were not limited to adjusting macronutrient proportions. Some studies evaluated the metabolic effects of different carbohydrate types in critical illness.

Kumbier et al. [32] conducted a randomized, controlled, double-blinded crossover clinical trial to assess whether the presence of fructose interferes with glycemic variability. They randomly assigned patients to receive one of two diabetes-specific diets (fructose-based versus maltodextrin-based) to evaluate the impact of these formulas on glucose variability. The study results indicated no difference in glycemic variability among critically ill patients who used diabetes-specific enteral formula, with or without fructose. Egi et al. [33] also conducted a pilot randomized crossover trial to assess the impact of an enteral formula based on isomaltose on glucose control. The primary point of the study was to determine the average and highest blood glucose levels during the feeding period. The levels were found to be significantly lower in the isomaltose group. They also reported a lower variability in glucose levels in the isomaltose group compared to the control group.

Adolph's study [34] demonstrated that parenteral nutrition using a glucose solution and lipid emulsion regimen led to lower blood glucose concentration and insulin activity compared to parenteral nutrition using a fructose solution and lipid emulsion.

Insights into nutritional supplements

Micronutrients and conditionally essential amino acids like glutamine offer potential immunomodulatory effects, prompting research into their use for managing stress hyperglycemia in critically ill patients.

- Promising metabolic effects of loading dose 7.5 g of magnesium sulfate IV infusions in patients with stress hyperglycemia [41].
- The controversial effect of vitamin D supplementation regarding the route and duration of administration was observed in managing SIH [42, 43].
- Administration of a single high-dose vitamin D3 (500,000 IU) within a week of admission for patients with 25-hydroxy-vitamin D plasma concentrations below 12.5 ng. ml^{-1c} [44].
- Alanyl-glutamine (Ala-Gln) supplementation (0.5 g/kg/day) attenuated hyperglycemia and improved insulin sensitivity in ICU patients without multiple organ failures or septic shock [45–49].
- Supplementation with L-carnitine and α-lipoic acid (ALA) has also been shown to improve insulin resistance in separate studies, as measured by HOMA-IR [50, 51].
- Two different herbal formulations modified HuangLian JieDu decoction and fenugreek seed powder had promising effects on managing SIH [52, 53].

Magnesium sulfate

Heidary et al. [41] conducted a randomized clinical trial to evaluate the effect of a magnesium loading dose (7.5 g of magnesium sulfate in 500 mL normal saline as an intravenous infusion over an 8-h period) on insulin resistance in patients with stress hyperglycemia. Their results suggested significant differences between the group that received magnesium and the placebo group in the mean changes of their blood glucose concentration from baseline. Furthermore, the researchers noted significant improvements in insulin resistance indices in the group that received magnesium compared to the group that received a placebo.

Vitamin D

Data from studies investigating the effects of vitamin D supplementation on glycemic indices and insulin resistance in non-ICU patients are controversial. Some of these studies showed positive effects of vitamin D supplementation on decreasing fasting glucose, HbA1C, or insulin resistance [54], while others could not confirm these findings [55–57].

Alizadeh et al. [42] studied the effects of vitamin D supplementation on stress hyperglycemia in critically ill patients. Patients in the vitamin D group received a single dose of 600,000 IU of vitamin D3 as an intramuscular injection at the time of recruitment. On day 7, patients in the vitamin D group had significantly higher levels of vitamin D and adiponectin in their plasma, which serves as a biomarker of insulin sensitivity, compared to the placebo group. However, no significant differences were observed in the serum glucose, insulin, HOMA-IR, and HOMA-AD levels between the groups. The researchers attributed the inadequate and non-significant response to vitamin D supplementation to the slow absorption of vitamin D when administered intramuscularly and the short duration of the study, which may not be sufficient to demonstrate any potential therapeutic benefits of vitamin D3 in managing stress hyperglycemia.

Besides, Paez et al. [43] showed that daily administration of 1000 international units of vitamin D plus 1000 mg of calcium reduced blood glucose concentration and undesirable events, such as hypoglycemia, defined as blood glucose levels below 100 mg/dL after 72 h. These two studies provide evidence of the potential therapeutic benefits of vitamin D3 in managing stress hyperglycemia. They also emphasize the need for additional research in this area, particularly regarding the most effective route of administration, duration of follow-up, and timing of vitamin D3 administration.

Although vitamin D deficiency is linked to poorer patient outcomes, the VITdAL-ICU study in 2014 found that regular administration of high-dose vitamin D did not improve hospital length of stay or 6-month mortality for critically ill patients with vitamin D deficiency. However, patients with severe deficiency may benefit. The European Society for Clinical Nutrition and Metabolism (ESPEN) suggests the administration of a single high-dose of vitamin D3 (500,000 IU) within a week of admission for patients with 25-hydroxy-vitamin D plasma concentrations below 12.5 ng. ml^{-1} [44].

Glutamine

In critical illness, the demand for glutamine may surpass the body's capacity to produce it. Glutamine improves nitrogen balance and may reduce protein catabolism.

Glutamine restores intracellular levels of glutathione and modifies heat shock proteins [58]. Furthermore, glutamine modulates fatty acid oxidation [59]. Several studies have evaluated the effects of 0.5 g/kg/day of Ala-Gln parenteral supplementation on glucose homeostasis for at least 5 days. Their results have shown that Aln-Gln supplementation attenuated hyperglycemia and improved insulin sensitivity in critically ill patients [45–49].

Apart from the metabolic effects of glutamine in critical illnesses, studies evaluating the clinical outcomes of glutamine supplementation in critically ill patients appear to be contradictory. Although some studies have demonstrated the beneficial or neutral effects of glutamine supplementation in critical illness [60–63], the results of the largest randomized controlled trial on glutamine supplementation in critically ill patients (REDOX) showed an increase in the patients' mortality rate [64]. To explain this controversy, we should consider that glutamine metabolism varies in different situations. REDOX utilized high doses of glutamine in ICU patients with multiple organ failures and septic shock, who exhibited a high level of inflammation in their bodies, the situation that immune cells may utilize a significant portion of the available glutamine [65]. This could potentially exacerbate the inflammatory response and reduce the patient's chances of survival. In addition, the complex glutamine metabolism in critically ill patients may result in unpredictable effects of glutamine supplementation [66]. Further studies are needed to unravel the glutamine metabolism in critically ill patients to identify patients who may benefit from glutamine supplementation.

Supplementation with L-carnitine and α-lipoic acid (ALA) has also been shown to improve insulin resistance, as measured by HOMA-IR, in separate studies [50, 51].

L-Carnitine

In another study, Nejati et al. [50] evaluated the effect of 1.5 g per day of L-carnitine supplementation for 6 days on patients with acute ischemic stroke during the early phase of critical illness. Their results revealed improved insulin resistance, as assessed by HOMA-IR, as well as decreased insulin concentrations and levels of C-reactive protein, which is an inflammatory marker, in these patients.

α-Lipoic acid (ALA)

Hejazi et al. [51] demonstrated the significant beneficial effects of a 10-day supplementation of 900 mg ALA on the severity of inflammation, measured by C-reactive protein levels, and the total antioxidant capacity in critically ill patients. These patients were expected to stay in the ICU for at least seven days and required enteral feeding. Their results also revealed that patients who received ALA supplementation had lower blood glucose levels and improved insulin sensitivity (measured by HOMA-IR) compared to the patients who received a placebo. However, the groups had no significant difference in clinical outcomes, such as the length of ICU/hospital stay, ICU/hospital mortality, 28-day mortality, and ventilator-free days.

Herbal formulas

Two studies evaluate the effects of supplementing two different herbal formulas, which have been found to be effective in traditional medicine for glycemic management in critically ill patients.

Kooshki et al. [52] conducted a randomized controlled clinical trial on 60 adult patients who were randomly divided into two groups. The intervention group received 3 g of fenugreek seed powder orally twice a day, in addition to their regular insulin therapy, for a duration of 10 days. Their data showed that the average glucose levels were significantly lower in the intervention group compared to the control group. Wang et al. [53] demonstrated that the use of modified HuangLian JieDu decoction (a well-known Chinese herbal remedy) as a

supplementary medication for early enteral nutrition led to a reduced occurrence of hyperglycemia and gastric retention in septic patients. They also reported that the duration of mechanical ventilation and ICU stay were significantly shorter in the intervention group compared to the control group. However, the 60-day mortality rate was not significantly different between the groups.

Two different herbal formulations modified HuangLian JieDu decoction and fenugreek seed powder had promising effects on managing SIH [52, 53].

Conclusions

While numerous RCTs have investigated nutritional strategies in critically ill patients, a definitive, one-size-fits-all approach remains elusive. Individual patient characteristics significantly influence optimal nutritional management, demanding personalized treatment plans.

Despite this ongoing quest for the "perfect" approach, several key recommendations offer demonstrable benefits for ICU patients. For hemodynamically stable individuals, early initiation of nutritional support within 24–48 h of critical illness onset is crucial. Continuous enteral nutrition typically serves as the preferred method. However, the specific route and modality should be carefully selected based on patient-specific factors such as care needs, nutritional status, and potential complications.

Intriguingly, the administration of diabetes-specific enteral formulas has shown promise in improving glycemic control and reducing insulin requirements. However, recent meta-analyses have not identified any definitive clinical advantages for this specific method.

Furthermore, research into targeted supplementation with individual nutrients like magnesium, vitamin D, and others suggests potential metabolic benefits in specific patient subgroups. However, limitations in study quality and insufficient data currently constrain our ability to confirm or refute their broader clinical significance.

In conclusion, the field of critical illness nutrition continues to evolve with ongoing research efforts. Although a universally optimal approach remains elusive, personalized strategies guided by individual patient characteristics and supported by emerging evidence represent the current best practice. Future high-quality research holds the key to further refining nutritional interventions and optimizing outcomes for critically ill patients.

Abbreviations

ALA	α-Lipoic acid
BMI	Body mass index
CRS	Carbohydrate-restrictive strategy
DM	Diabetes mellitus
DSFs	Diabetes-specific formulas
ESPEN	The European Society for Clinical Nutrition and Metabolism
HOMA	Homeostatic Model Assessment
ICU	Intensive care unit
IIT	Intensive insulin therapy
LE	Lipid emulsion
MUFA	Monounsaturated fatty acids
RCT	Randomized controlled trial
SF	Sequential feeding
SIH	Stress-induced hyperglycemia
STDF	Standard formulas
TPN	Total parenteral nutrition

Supplementary Information

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Supplementary Material 1.

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Authors' contributions

Fatemeh Rahimpour: investigation, methodology, visualization, writing—original draft preparation, and writing—review and editing. Malihe Nejati: investigation, methodology, visualization, writing—original draft preparation, and writing—review and editing. Shadi Farsaei: conceptualization, data curation, formal analysis, funding, acquisition, methodology, project administration, software, supervision, validation, visualization, writing—original draft preparation, and writing—review and editing. Azadeh Moghaddas: methodology, project administration, supervision, and writing—review and editing. Awat Feizi: formal analysis, methodology, software, supervision, and writing—review and Editing.

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Availability of data and materials

The data set used in the current study is available on request from (contact name/email id).

Declarations

Ethics approval and consent to participate

The institutional review board approved the employed methodologies, assigning the ethical code IR.MUI.MED.REC.1400.545. Consent to participate is not applicable.

Consent for publication

I, on the behalf of all authors, give my consent for the publication of our manuscript entitled "Nutritional modifications to ameliorate stress hyperglycemia in critically ill patients: A systematic review" to be published in the Egyptian journal of internal medicine.

Competing interests

No competing interest.

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