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Review article

Metabolic support challenges with obesity during critical illness

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ABSTRACT

Adiposity-based chronic disease, critical illness, and nutrition therapy increase the risk for overfeeding and worsened nutritional and clinical outcomes. Hypocaloric, high-protein nutrition therapy provides critically ill obese patients the opportunity to achieve net protein anabolism with a reduced risk for overfeeding-related complications. The intent of this review is to discuss the impact of obesity on clinical outcomes, describe the consequences of obesity that increase complications associated with nutrition therapy, provide the framework to develop a hypocaloric, high-protein regimen, review the scientific evidence to support this mode of therapy, and discuss its limitations. Practical suggestions for patient monitoring are also provided.

Introduction

Obesity has been described by numerous health organizations and societies as a disease [1]. Over the past 30 y, the global rates of adult and childhood obesity have doubled and adolescent obesity tripled [1]. Because of this epidemic [2], one-fourth to one-third of patients in the intensive care unit (ICU) in the United States are obese [3,4]. A prevalent erroneous belief exists that nutrition therapy may not be necessary for patients with obesity due to the presence of caloric abundance. Contemporary evidence of this misconception was recently reflected by a delay in the initiation of nutrition support for patients with obesity versus those who are not obese [5].

The metabolic management of obese patients has unique challenges because patients may experience adiposity-based chronic diseases as well as physiologic and metabolic complications that directly interface with nutrition support therapy. Patients often require interventions that are unique to their disease processes and dependent or independent of their obesity [6–8]. Because of these conditions, critically ill patients who are obese may require a parenteral or enteral nutrient prescription that is uniquely different than that for those who are not obese [6–8].

One common approach for hospitalized obese patients that has been recommended by recent American guidelines is the provision of hypocaloric, high-protein nutrition therapy [8,9]. Hypocaloric nutrition therapy may be defined as providing a caloric intake that is less than the energy expenditure. However, under the constraints of restricting caloric intake, a compensatory increase in protein intake is required to achieve a similar nitrogen balance of eucaloric feeding (i.e., caloric intake matches energy expenditure) or hypercaloric therapy (i.e., caloric intake is in excess of energy expenditure) [10]. Thus, the intent of hypocaloric, high-protein nutrition therapy is to reduce the risks of overfeeding complications and avoid worsening any preexisting metabolic perturbations that are associated with obesity as compounded by critical illness.

A second objective of this mode of therapy is to potentially achieve net protein anabolism or reduce marked protein catabolism and negative nitrogen balance that is associated with critical illness despite the constraints of restricting caloric intake [8–10]. Diligence in monitoring to evaluate the safety and efficacy of the nutrition support prescription and the tenacity to adjust the regimen on the basis of patients' metabolic response is of paramount importance for critically ill obese patients who receive hypocaloric, high-protein nutrition therapy [6–11].

Defining obesity, clinical outcomes, and the obesity paradox

Obesity, by definition, is the accumulation of excessive body fat that leads to comorbidities and impacts the health of the individual.

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Body mass index (BMI), despite its significant limitations due to the lack of assessment of muscle mass contribution to body weight, is the most commonly used tool in conventional clinical practice to assess for the presence of obesity. The severity of obesity is organized by classes and a higher BMI score indicates more severe disease as indicated by the development of adiposity-related complications. However, numerous studies in the past decade have suggested that patients who are overweight (BMI >25–29.9 kg/m^2) or mild-to-moderately obese (BMI >30 and <40 kg/m^2) without significant adiposity-based diseases have better clinical outcomes than those who are considered malnourished (BMI <18.5 kg/m^2) or morbidly obese (BMI >40 kg/m^2) [12].

The prevailing theme from these studies is that an inverse, J-shaped curve may be present when relating BMI to survival. Malnourished patients with a low BMI score and those with severe class III obesity (BMI >40 kg/m^2) would be expected to have the worse outcomes whereas those with a normal body weight and those who are overweight or mild-to-moderately obese would have better outcomes [13–18] This phenomenon has been termed the obesity paradox. The etiologies for this presumed paradox are not clear but numerous studies suggest that adipose tissue is a functional organ that is capable of altering the metabolic and immunologic response to sepsis or stress.

Adipose-derived leptin has been shown to increase immune response and improve bacterial clearance [19]. Other adipokines such as lipoproteins, apoproteins, and eicosanoid-derived resolvins and protectins may neutralize endotoxins, stimulate the clearance of inflammatory debris, and have antiinflammatory effects [20]. However, despite this mounting evidence, the obesity paradox is still considered controversial. Because of the heterogeneity in clinical outcomes across the BMI spectrum, the obesity paradox may not be a real phenomenon but rather a reflection of selection bias and errors in study design [12]. One important factor that is usually ignored in studies that examine the impact of metabolic complications of obesity on clinical outcomes is the influence of nutritional intervention. A recent study alludes to the value of evaluating nutrition intervention on the obesity paradox phenomenon. In a large retrospective cohort of more than one million patients, a survival advantage for overweight and obese patients was observed [21]. However, when examining the differences in hospital mortality between obese and non-obese groups of patients who were prescribed early enteral nutrition therapy, these outcome differences were minimized [21].

Irrespective of a presumed obesity paradox, a plausible question remains whether BMI alone is diagnostically sufficient to identify patients with obesity who are at risk to suffer complications during critical illnesses without consideration for the presence of adiposity-related chronic diseases or sarcopenia. Clinical outcomes may be worse and nutrition therapy should be targeted to reduce adverse consequences from the presence of adiposity-related comorbid conditions such as diabetes, insulin resistance, hyperglycemia, hypoventilation syndrome, or other associated metabolic perturbations from obesity.

Sarcopenic obesity is another important but often ignored consideration. Sarcopenia is evidenced by a loss of lean muscle mass and resultant decline in muscle strength [22] and is more difficult to detect in obese patients because traditional physical assessment methods are limited by the presence of excessive body fat. The presence of impaired mobility before hospitalization or advanced age may contribute to a high index of suspicion with regard to the presence of sarcopenia [6]. The detection of sarcopenia in obese patients is important because sarcopenia has been associated with detrimental clinical outcomes including poorer functional status, dysglycemia, a higher incidence of chemotherapy toxicity, and worsened survival [23–25].

Obesity and complications associated with nutritional therapy

When developing a safe and effective nutrition regimen for critically ill patients who are obese, modifying the regimen on the basis of any adipose-associated comorbidities the patients may be experiencing is mandatory. The greatest concern is to not overfeed obese patients because complications from overfeeding extend beyond just a simple amplification in preexisting, abundant, caloric reserves. Therefore, the nutrition regimen may need to be modified for hyperglycemia, hypertriglyceridemia, hypercapnia, congestive heart failure, or nonalcoholic fatty liver disease. Modifications of the nutritional intervention can be complicated by the presence of multiple concurrent comorbidities that are common for many critically ill patients with obesity.

Hyperglycemia commonly occurs when the glucose intake exceeds 5 mg/kg/min [26]. Patients with all classes of obesity may be insulin resistant, but it is most common in those who have a BMI exceeding 40 kg/m^2 [27]. Patients with obesity are prone to hyperglycemia even at lower caloric and glucose intakes [27,28]. Critically ill patients with sepsis or traumatic injuries experience a post-receptor insulin resistance resulting in substantial hyperglycemia [29]. Thus, when obesity, critical illness, and nutrition therapy are compounded together, hyperglycemia is a prevalent complication that requires vigilant management which can be challenging [30]. This difficulty is exemplified by critically ill trauma patients with obesity-related diabetes mellitus who required a continuous intravenous insulin infusion experienced a greater hyperglycemic index and greater blood glucose concentration variability and spent less time in the target blood glucose concentration range than non-diabetics [31].

Hyperlipidemia and particularly hypertriglyceridemia occurs more often in patients who are obese versus those who are not. This may be problematic for patients who are given intravenous lipid emulsion as part of the parenteral nutrition therapy or propofol (10% soybean oil-based, lipid emulsion as the drug carrier solution). Severe hypertriglyceridemia from impaired lipid emulsion clearance may impair the immune function, decrease reticuloendothelial system clearance, cause hepatic fat accumulation, and potentially induce acute pancreatitis.

Improvements in glycemic control with insulin therapy will often result in the near normalization of serum triacylglycerol concentrations for the majority of patients with insulin-dependent diabetes mellitus [32]. For patients with non–insulin-dependent diabetes mellitus, hypertriglyceridemia does not consistently improve despite glycemic control [32] and lipid emulsion clearance may remain impaired. A couple of viable options to provide parenteral nutrition to obese patients with hypertriglyceridemia is the substitution of soybean oil-based lipid emulsions with alternative multiple-source oil emulsions [33] or provide parenteral nutrition solutions without lipid emulsion. Fat-free parenteral nutrition as a hypocaloric, high-protein regimen may be safely given for several weeks to obese patients without biochemical or clinical evidence of essential fatty-acid deficiency [34].

Despite these data, the apparent availability of endogenous fat for energy during critical illness in patients who are obese has been challenged [35]. Critically ill trauma patients with obesity who were studied within 4 d after hospital admission and before the initiation of nutrition therapy indicated reduced lipolysis and net fat oxidation [35]. Conversely, in a case series of seriously ill obese patients, serial respiratory quotient measurements indicated that 68% of non-protein energy was derived from endogenous fat

oxidation during the provision of hypocaloric, high-protein, fat-free parenteral nutrition [36]. Taken together, critically ill obese patients may exhibit a transient impairment in lipolysis and fat oxidation that occurs early after the acute traumatic event but resolves quickly during patients' hospital stay.

The presence of obesity has been associated with mechanical factors that lead to changes in pulmonary function [37] and the requirement for prolonged mechanical ventilation [6,38]. Obesity hypoventilation syndrome, which is characterized by hypercapnic respiratory failure and hypoventilation, occurs in 10% to 20% of patients [3,39]. These changes in pulmonary function result in greater minute ventilation requirements and excessive caloric intake can worsen hypercapnia [40,41]. Increased carbon dioxide production occurs when the total energy intake exceeds 1.3 times the predicted energy expenditure [40,41]. Caution with regard to the amount of calories that are given to ventilator-dependent patients with chronic obstructive pulmonary disease or obesity hypoventilation syndrome is pivotal.

Because of the requirement for an increased circulating blood volume due to excessive body mass, obese patients are at risk for hypovolemic shock [42] and can develop myocardial hypertrophy and decreased compliance that leads to congestive heart failure and total body fluid accumulation [39,43,44]. Thus, some critically ill patients who are obese may require fluid restriction. Finally, critically ill patients with morbid obesity are also at risk for non-alcoholic fatty liver disease and hepatic steatosis and particularly those patients with a prolonged history of hypertension, hyperlipidemia, and diabetes [45,46].

Overfeeding has long been established as a common complication of parenteral nutrition therapy that results resulting in fatty infiltration of the liver and hepatic steatosis [47], which could worsen patients' fatty liver disease that is associated with the obesity. Therefore, not overfeeding critically ill patients who are obese is critical. Excessive caloric intake may worsen concurrent adiposity-related complications or lead to the development of overfeeding complications that are analogous to those observed in non-obese patients.

Defining energy and protein requirements

Wide variability and lack of precision to estimate caloric requirements makes the avoidance of overfeeding in critically ill obese patients challenging [8]. This inaccuracy is due to differing amounts of muscle mass as well as diseases and conditions that can variably alter energy expenditure. Because of the unavailability of indirect calorimetry for most institutions, the 2013 American Society of Parenteral and Enteral Nutrition guidelines for the nutrition support of hospitalized adult patients with obesity [8] recommends the use of the Penn State equation or the modified Penn State equation (for patients age >60 y) to estimate energy expenditure of ventilator-dependent, critically ill patients. However, these equations are also limited in their accuracy [8].

Elwyn and Kinney pioneered the concept that energy and protein should be considered separately in designing feeding regimens that depend on the desired body composition outcome goals [10]. Their data, which were derived from unstressed, depleted patients, indicated that nitrogen equilibrium or a positive nitrogen balance could be achieved with either a high-protein/low-calorie intake, moderate-protein/moderate-calorie intake, or low-protein/high-calorie regimen [10]. However, despite a similar nitrogen balance among the study groups, these regimens would be anticipated to result in different body composition changes. On the basis of early studies by Hill et al. [48], the high-protein/low-calorie regimen would result in a gain of lean body mass with body fat loss whereas the low-protein/high-calorie regimen would lead to a gain in body fat at the expense of loss of lean body mass. From this stratagem, the concept of hypocaloric, high-protein nutrition therapy for hospitalized obese patients was derived [36,49].

The attainment of a positive nitrogen balance is often not possible during the acute phase of critical illness [50]. Body protein loss during extreme critically ill conditions such as multiple traumatic injuries may exceed two to three times that observed during unstressed starved conditions [50]. In the United States, clinicians often provide a high-protein intake (e.g., 1.5 to 2.5 g/kg/d) for patients who experience this level of catabolism. However, the marked increase in whole-body catabolism cannot be overcome solely by an increase in nutrient intake because nutrition therapy predominantly increases whole-body synthesis.

Marked protein catabolism does not abate until the stress of critical illness resolves [51,52]. Even though total-body protein content declines during critical illness despite nutrition therapy [53], net protein catabolism is substantially reduced compared with when not given nutrition therapy [45,46] and would favor the concept of increasing protein intake during extreme catabolic conditions. However, even an aggressive protein intake of 2 to 2.5 g/kg/d only achieved nitrogen equilibrium (nitrogen balance of 0 ± 5 g/d) in approximately half of a large series of patients during the first 14 d postadmission to the trauma ICU [50].

Conversely, increasing the caloric intake from 82% to 118% to 148% of the measured resting energy expenditure while maintaining the protein intake constant at approximately 1.7 g/kg/d was futile toward the improvement of the nitrogen balance because a balance of approximately-8 g/d remained unchanged with the differing caloric intakes. Urinary 3-methylhistidine excretion (i.e., marker of skeletal muscle catabolism) in critically ill patients with traumatic injuries was also unchanged with the escalation of non-protein caloric intake [54]. Increasing the caloric intake above 1.2 times the measured resting energy expenditure has been demonstrated to result in a significant increase in total body fat without further attenuating erosion in lean body mass for critically ill, thermally injured patients [55]. These data support the concept that protein has a more profound effect than non-protein calorie intake on net protein catabolism, nitrogen balance, and loss of body protein mass during critical illness. Increasing non-protein calories tends to worsen adiposity-related complications and increases the risk of overfeeding. Since prudent metabolic care of critically ill patients includes avoiding adverse consequences of overfeeding in an at-risk population, these data indicate that a more tactical approach to therapeutic nutrition intervention would be employing the strategy of hypocaloric, high-protein nutrition therapy for critically ill patients who are obese.

Evidence to evaluate efficacy and safety of hypocaloric, high-protein nutrition therapy in critically ill patients who are obese

Before discussing the evidence in support of the safety and efficacy of hypocaloric, high-protein nutrition therapy, permissive underfeeding must be differentiated from hypocaloric, high-protein nutrition therapy. The clarification of these terminologies is essential because clinicians inappropriately use the same permissive underfeeding terminology for these two distinctively different therapies, which causes confusion between the two techniques. Permissive underfeeding indicates that the patient is intentionally allowed to receive less than what is considered the goal intake for both calories and protein. However, the intent of hypocaloric, high-protein nutrition therapy is to provide only a calorie deficit while ensuring an adequate protein intake. Since the caloric intake is reduced, a higher compensatory protein intake is mandatory to

achieve net protein anabolism or nitrogen equilibrium. One observational study discovered the consequences of permissive underfeeding to hospitalized patients with obesity [56]. When inadequate protein intake (46 g of protein/d or 0.4 g/kg/d) was given to a subset of obese patients with a hypocaloric energy intake (1000 kcal/d or 9 kcal/kg/d), the 60 d mortality was worse [56]. Thus, permissive underfeeding with a significant concurrent deficit of calories and protein should be avoided altogether in critically ill patients with obesity.

Table 1 summarizes the literature on hypocaloric, high-protein nutrition therapy for critically ill patients who are obese. In the late 1970s, Jeejeebhoy [49] contributed to the infancy of hypocaloric, high-protein nutrition therapy under the premise of intravenous, protein-sparing therapy in which intravenous amino acids without a non-protein caloric source were given to a case series of patients with "sufficient body fat stores" to justify the use of hypocaloric caloric regimens. Patients were described as moderately ill but with neither postoperative nor with postacute injury. The investigators found that if patients were given adequate protein intake (e.g., 1.8 g/kg ideal body weight [IBW]/d as opposed to 0.8 g/kg IBW/d), a positive nitrogen balance could be achieved.

Dickerson and Mullen reported on the first case series with use of hypocaloric, fat-free, high-protein, parenteral nutrition therapy for seriously ill surgical patients with obesity (Table 1) [36]. Surgical patients with complications of sepsis were given a parenteral nutrition regimen that was comprised of a total caloric intake of approximately 70% of measured resting energy expenditure and 2.1 g/kg IBW/d of protein. The patients achieved a positive nitrogen balance and exhibited positive clinical outcomes as evidenced by a closure of the fistulae, resolution of abscess cavities, and wound closure. This case series was then followed by two prospective, randomized, controlled trials of surgical patients with obesity in ICU and non-ICU settings at the Ohio State University Hospital. [28,57].

In these two studies, a hypocaloric regimen was compared with a higher calorie parenteral nutrition regimen while keeping the protein intakes similar at 2 g/kg IBW/d (Table 3). Positive nitrogen balances were observed for both the eucaloric and hypocaloric groups in both studies. The hypocaloric group required less insulin but did not experience a difference in clinical outcomes [26]. In addition, this difference in insulin requirements is difficult to evaluate because this study was performed before our current knowledge of the importance of more rigorous glycemic control for the clinical outcomes of critically ill patients [30].

Until 2002, published investigations with regard to hypocaloric, high-protein nutrition therapy for patients with obesity were done via the administration of parenteral nutrition. The lack of literature for enteral delivery of hypocaloric, high-protein nutrition therapy was most likely attributable to the advantage of parenteral over enteral nutrition because each macronutrient can be independently prescribed. Providing a hypocaloric, high-protein, enteral nutrition regimen was more difficult than a parenteral nutrition at that time due to the lack of commercially unavailable, ultra-high proteins that contain enteral formulas (e.g., 1 kcal/mL contains 92 g of protein/L) and are commercially available today. The primary limitation with enteral nutrition is that commercially available formulations are only available in fixed macronutrient concentrations. Thus, the use of protein supplements concurrently with a reduction in enteral formula feeding rate in combination with high protein-containing formulas (e.g., 62–64 g of protein per L) may be necessary to achieve the intended target caloric and protein intakes if ultra-high protein-containing formulas are not available at the reader's institution.

Dickerson et al. were the first to examine the impact of hypocaloric (versus eucaloric) enteral feeding in critically ill patients with obesity (Table 1) [58]. Patients received either hypocaloric feeding (<25 kcal/kg IBW/d) or eucaloric feeding (25–30 kcal/kg IBW/d). The protein goals were 2 g/kg IBW/d for both groups. Both caloric groups experienced similar negative nitrogen balances due to the equivalent protein dosing and hypercatabolic state after multiple traumatic injuries. However, unlike the previous studies that indicated no difference in clinical outcomes between isonitrogenous hypocaloric and eucaloric feeding groups [27,57], isonitrogenous hypocaloric feeding was associated with improved clinical outcomes including a decreased length of ICU stay, decreased duration of antibiotic therapy, and a trend toward decreased ventilator days and hospital length of stay [58]. Because this small, retrospective cohort study is the only study to date to infer improved clinical outcomes with hypocaloric, high-protein feeding for critically ill obese patients, a confirmation of these data by a large prospective, randomized, controlled trial is warranted.

From these data, the recommendations from the 2013 American Society for Parenteral and Enteral Nutrition guidelines for hospitalized patients with obesity [8] and the 2016 joint Society of Critical Care Medicine/American Society for Parenteral and Enteral Nutrition guidelines [9] for the provision of nutrition therapy to adult critically ill patients with obesity were derived. Patients are recommended to receive 50% to 70% of estimated energy needs or <14 kcal/kg actual weight per day or <25 kcal/kg IBW/d with a protein intake of 1.2 g/kg actual weight per day or 2 to 2.5 g/kg IBW/d. This author recommends that an initial protein intake of at least 2 g/kg IBW/d be given to patients with a BMI of 30 to 39.9 kg/m^2 and 2.5 g/kg IBW/d to those who have a BMI >40 kg/m^2 with an adjustment of the goal protein intake as reflected by the results of the nitrogen balance studies. This author has adopted an empiric ceiling protein dose of 3 g/kg IBW/d under conditions of extreme catabolism and a markedly negative nitrogen balance [7,50]; however, the nutritional and clinical ramifications of this dosage require further study.

Specialized considerations to the use of hypocaloric, high-protein nutrition therapy

Some subpopulations of hospitalized patients with obesity may require an adjustment in macronutrient design or protein intake. The subpopulations of interest include older patients, those with class III obesity, and renal or hepatic failure.

Older patients

Decreased sensitivity of muscles to anabolic stimuli including amino acids occurs during aging but this relative resistance can be overcome with a higher protein intake in normal healthy subjects [59] as well as during critical illness [60]. One study questioned whether older (e.g., age >60 y) patients with obesity who are hospitalized can effectively respond to hypocaloric, high-protein nutrition therapy due to this anabolic resistance phenomenon [61]. Despite similar protein and energy intakes, the investigators noted a worsened nitrogen balance in the older patient group compared with younger patients during hypocaloric, high-protein feeding [61]. Because high-protein intakes are necessary to achieve an anabolic effect during energy-restrictive diets, whether protein intake was adequate in that study is questionable.

A follow-up investigation revealed similar nitrogen balances between younger (age 18–59 y) and older (age ≥60 y) critically ill patients when both age groups were given protein intakes of at least 2 g/kg IBW/d [7]. One concern of providing high-protein intakes to older patients as required for hypocaloric, high-protein nutrition therapy is the potential for azotemia. Aging is associated

Table 1
Summary of studies on hypocaloric, high-protein feeding in hospitalized obese patients

Author, year	Patient Population	Groups	Route	No.Pts	WT/BMI (kg, kg/m^2)	Total caloric intake (kcal/kg/d)	Protein intake (g/kg IBW/d)	Nitrogen balance (g/d)	Other nutritional outcomes	Clinical outcomes	Study limitations
Greenberg and Jeejeebhoy, 1979	GI diseases	Low protein vs. high protein	PN	6	Not given (described as "sufficient fat stores")	3 IBW	0.83	-3.7	Lower plasma glutamine and ketones in high protein intake group	Not evaluated	Small study; nonrandomized; population details lacking; no nonprotein kcals given
				6		7 IBW	1.83	+1.5			
Dickerson, 1986	Surgical, infected	Case series	PN	13	127 ± 60 –	25 IBW	2.1 ± 0.6	+2.4 ± 1.9	Incr Alb, incr TIBC, decr RQ, weight loss	Healed wounds, closed fistulae	Small case series; no comparative population
Burge, 1994	Surgical	Hypocaloric vs. eucaloric	PN	9	90 ± 12.5 33 ± 6	22 IBW	2.0 ± 0.6	+1.3 ± 3.6	Weight loss; lower RQ with hypocaloric group	Not evaluated	Small study; questionable difficulty with indirect calorimetry measurements
				7	102 ± 20 35 ± 4	42 IBW	2.2 ± 0.4	+2.8 ± 6.9			
Choban, 1997	Surgical, SICU	Hypocaloric vs. eucaloric	PN	16	97 ± 19 36 ± 5	22 IBW	2.0 ± 0.1	+4.0 ± 4.2	No difference in Alb, SUN, weight; incr insulin requirements for eucaloric group	No difference in mortality, LOS	Small study; mixed ICU and non-ICU patients
				14	90 ± 17 34 ± 6	36 IBW	2.0 ± 0.1	+3.6 ± 4.1			
Liu, 2000	Surgical	Age < 60 y Age > 60 y	PN	18	97 ± 16 34 ± 5	18 CBW	1.8 ± 0.4	+3.4 ± 3.9	No difference in Alb, transferrin, weight	No difference in morbidity or mortality	Small study; retrospective;
				12	84 ± 20 31 ± 5	18 CBW	1.9 ± 0.3	+0.2 ± 5.0			
Dickerson, 2002	Trauma ICU	Hypocaloric vs. eucaloric	EN	28	118 ± 41 41 ± 14	22 IBW	2.0 ± 0.5*	-2.7 ± 5.9	Both groups increased PA, no change Alb	Decreased ICU stay, decreased antibiotic days, trending decrease in ventilator days for hypocaloric group. No diff in mortality	Small study; retrospective
				12	102 ± 36 36 ± 12	30 IBW	2.0 ± 0.4*	−1.4 ± 5.8			
Choban and Dickerson, 2005	Surgical, SICU, Trauma ICU	BMI 30–39.9	PN & EN	48	97 ± 31 35 ± 9	Regression analysis for determination of protein requirements to achieve nitrogen equilibrium from 2 different medical centers		Protein intake required to achieve nitrogen equilibrium: ICU patients: BMI 30–39.9: ~2 g/kg IBW/d BMI > 40: ~2.5 g/kg IBW/d Non-ICU patients: BMI 30 to 39.9: ~1.7 g/kg IBW/d BMI > 40: ~1.8 g/kg IBW/d		Not evaluated	ICU and non-ICU patients; retrospective
		BMI >40		22	122 ± 33 44 ± 12						
Dickerson, 2013	Trauma ICU	<60 y	PN & EN	41	105 ± 21 35 ± 5	18 IBW	2.3 ± 0.2*	-4.9 ± 9.0	Similar changes in PA; higher SUN for older patients	No difference in ICU LOS, ventilator days, hospital LOS, mortality	Retrospective
		≥60 y		33	105 ± 26 35 ± 6	21 IBW	2.3 ± 0.3*	−3.2 ± 5.7			

Alb, serum albumin concentration; BMI, body mass index; CBW, current body weight; decr, decreased; EN, enteral nutrition; GI, gastrointestinal; IBW, ideal body weight; ICU, intensive care unit; Incr, increased; LOS, length of stay; No., number of; NB, nitrogen balance; PA, serum prealbumin concentration; PN, parenteral nutrition; Pts, patients; RQ, respiratory quotient; SICU, surgery intensive care unit; SUN, serum urea nitrogen concentration; TIBC, total iron binding capacity; yo, years old

* during the NB study.

with a decline in renal function. Although the decrease in glomerular filtration rate that occurs with aging is not severe enough to elicit symptoms of renal failure [62], concern is often expressed by clinicians about prescribing higher aggressive protein intakes. Older patients experience a greater mean serum urea nitrogen concentration than the younger patients (30 ± 14 mg/dL versus 20 ± 9 mg/dL; $P = 0.001$) during hypocaloric, high-protein nutrition therapy [7] but these differences were not clinically relevant. However, of note, a minority of older patients (n = 4 or 12% of the population) experienced asymptomatic serum urea nitrogen concentrations >60 mg/dL. Thus, older patients may be at greater risk to develop azotemia when given high-protein intakes and should be closely monitored.

Class III obesity

Choban and Dickerson [27] combined their databases from previous studies [28,57,58] and examined the impact of severity of obesity on nitrogen accretion. Their study indicated that critically ill patients with Class III obesity required approximately 2.5 g/kg IBW/d of protein to achieve nitrogen equilibrium compared with approximately 2 g/kg IBW/d for those with class I or II obesity [27]. Lower protein intakes were sufficient to achieve nitrogen equilibrium for non-critically ill patients. The etiology for why patients with class III obesity require more protein may be due to potential differences in anabolism as a result of insulin resistance [63] or inaccuracy of IBW as an estimate of total body-protein content for protein dosing [64]. Further study with regard to the mechanistic implications of this phenomenon is warranted.

Hepatic/renal disease

Although the current guidelines infer that protein restriction may not be necessary for patients with renal or hepatic disease [9], ceiling protein doses for these subpopulations have not been established. Patients with significant renal or hepatic disease may not be able to tolerate a large protein intake due to impending uremia or worsening encephalopathy. The protein intake may need to be adjusted on the basis of change in serum urea nitrogen concentration, evidence of uremia, frequency and type of dialysis, or worsening of encephalopathy. Further research is necessary to define optimal caloric and protein intake for obese patients with significant advanced hepatic or renal disease.

Practical considerations to implement hypocaloric, high-protein nutrition therapy

Practical methods to deliver a hypocaloric, high-protein nutrition regimen successfully require creativity on the part of the clinician, especially when prescribing enteral nutrition. Table 2 illustrates a case scenario to develop this type of regimen for both parenteral and enteral nutrition therapies. However, the regimens that were developed in this case scenario may vary depending on the availability of commercial products at the reader's institution. In addition, the regimens provided are not the only methods to achieve this type of therapy for critically ill obese patients. Also, for caloric dosing, a temporary delay in advancement of non-protein caloric intake may be reasonable if a patient experiences complications that are associated with glucose/carbohydrate (e.g., hyperglycemia, hypercapnia, and hypertriglyceridemia) if the protein dosage is adequate. An adjustment of the initial protein goal intake may also need to be altered depending on the results of the nitrogen balance determination or development of new-onset organ dysfunction.

A hypocaloric, high-protein parenteral nutrition regimen is easier to prescribe than enteral nutrition because each macronutrient can be independently prescribed. The primary limitation to develop a parenteral nutrition regimen relates to the availability of commercially available macronutrient ingredients to compound the parenteral nutrition solution. Examples of different prescribing methods for parenteral nutrition that would meet these caloric and protein goals are shown in Table 2.

If a patient must be restricted from fluid, choosing the most concentrated commercially available solutions to compound the parenteral nutrition solution would be prudent. In the United States, this would entail compounding the solutions using 70% dextrose, 15% or 20% amino acids, and 20% or 30% lipid emulsion. Unfortunately, due to cost considerations, not all hospital pharmacies have the most concentrated macronutrient solutions to compound a fluid-restricted base formula. At the current time, the use of ready-to-hang, multichamber, parenteral solutions and be able to develop a hypocaloric, high-protein nutrition regimen without supplemental amino acid solutions that would have to be given concurrently with a dextrose-amino acid-lipid solution is somewhat impractical.

For enteral nutrition, providing a hypocaloric, high-protein regimen may be technically more difficult than a compounded parenteral nutrition solution because enteral formulas are only available in fixed macronutrient concentrations. An exception would be if an ultra-high protein, enteral formula (e.g., 1 kcal/mL and 92 g of protein/L) was available at the reader's institution, which often results in the development of a goal formula rate (Table 4), particularly if the patient has a BMI <40 kg/m^2. For those institutions that do not have this type of enteral formula on formulary, achieving these goals would require using the highest protein formula available with the addition of concurrent protein boluses (Table 2).

Metabolic monitoring

Patients should be closely monitored to ensure efficacy in addition to avoidance of potential complications that are associated with overfeeding [6,65]. Worsening blood glucose concentrations or hypercapnia without ventilator setting changes may often reflect overnutrition and caloric intake excess. Glycemic control is of paramount importance for patients with diabetes mellitus or stress-induced hyperglycemia. This is usually accomplished by providing a low carbohydrate/dextrose-containing nutritional regimen with blood-glucose monitoring throughout the day and accompanied with adjunctive insulin therapy [30,31,66,67]. If the patient is ventilator-dependent, evidence of new-onset hypercapnia via arterial blood gas measurements should be evaluated with respect to the nutritional regimen. Although serum liver function tests have been used to assess liver dysfunction due to overfeeding with parenteral nutrition, these tests are often unreliable in the short-term critical care setting. As a result, the assessment of obese patients for worsening fatty liver disease during nutrition therapy is problematic without more extensive radiologic or histologic data and these tests are usually not performed in routine clinical practice. Therefore, the monitoring of serum electrolytes, urea nitrogen, and triglycerides is necessary. Some clinicians monitor serial serum prealbumin concentrations; however, the interpretation of changes is often confounded because concentrations are decreased by the presence of stress, infection, and inflammation. As a result, serum C-reactive protein that is obtained concurrently with prealbumin concentrations have been employed to serve as a point of reference to interpret changes in serum prealbumin concentrations.

Some clinicians have used body weight changes to assess efficacy [28,57]. However, fat weight loss should be only regarded as a

Table 2
Development of a hypocaloric, high protein nutrition parenteral or enteral nutritional regimen

Nutrition method	Macronutrients	Rate	Calorie and protein intakes
Parenteral Nutrition: Concentration-based D10W amino acids 8% lipids 2%	D10 W amino acids 8% lipids 2%	75 mL/hr	1638 kcals or 24kcal/kg IBW 144 g protein or 2.1 g protein/kg IBW
Parenteral Nutrition: ASPEN Safe Practices	Dextrose 200 g, amino acids 140 g Lipids 40 g/d	75 mL/hr	1640 kcals or 24kcal/kg IBW 140 g or 2.1g protein/kg IBW
Enteral formula type	**Macronutrient concentration**		
Ultra-high protein	1 kcal/mL 92 g protein/L	70 mL/h	1680 kcals or 25 kcal/kg IBW 155 g or 2.3 g protein/kg IBW
Ultra-high protein	1 kcal/mL 92 g protein/L	65 mL/h	1560 kcals or 23 kcal/kg IBW 144 g or 2.1 g protein/kg IBW
High protein	1 kcal/mL 64 g protein/L	55 mL/h	1720 kcals or 25 kcal/kg IBW 144 g or 2.1 g protein/kg IBW
Protein boluses	Protein* 30 g twice daily		
High protein	1 kcal/mL 64 g protein/L	50 mL/h	1600 kcals or 24 kcal/kg IBW 137 g or 2.0 g protein/kg IBW
Protein boluses	Protein* 30 g twice daily		

ASPEN, American Society for Parenteral and Enteral Nutrition; BMI, body mass index; IBW, ideal body weight
Patient case: A 40-y old male, weight 110 kg, height 173 cm, IBW 68 kg, BMI 36.8 kg/m^2, normal renal and hepatic dysfunction, without hyperglycemia, hypertriacylglycerolmia, or a history of diabetes mellitus
Macronutrient nutritional goals: Energy (20–25 kcal/kg IBW/d or 1360–1700 kcals/d) and protein (2–2.5 g/kg IBW/d or 136–170 g/d)
* Many protein sources contain sweeteners and additives that increase the caloric content beyond the anticipated 4 kcal/g of protein. Based on the product used at the author's institution, the protein supplements contain an additional 80 kcal for every 30 g protein dose. Some institutions use liquid protein sources for bolus protein dosing while others use protein powder and mix with water then give as a bolus.

welcome secondary benefit and not the primary mission for hypocaloric, high-protein nutrition therapy during critical illness. Despite significant net fat oxidation as measured by indirect calorimetry, during hypocaloric high-protein feeding, no significant ketonuria was evident [36]. However, changes in body weight are unreliable in the critical care setting due to fluid perturbations that are associated with critical illness and fluid resuscitation. Strict attention to daily fluid intake and losses as well as a physical inspection of the patient for evidence of volume overload or dehydration including radiologic or hemodynamic monitoring when necessary or available is warranted.

One potential objective marker to assess undernutrition may be reflected by nitrogen balance [68]. A substantially negative nitrogen balance may indicate inadequate protein intake with the exception of extremely catabolic conditions during critical illness [7,36,50,58–60]. However, nitrogen balance has been questioned as to its validity as a marker to assess protein requirements for critically ill patients due to its limitations and assumptions [68] but a small number of studies indicate that an improvement in nitrogen balance is associated with improved clinical outcomes [69–71].

Conclusions

Because critically ill patients with obesity are susceptible to worsening of hyperglycemia, hypercapnia, and fatty liver disease, hypocaloric high-protein nutrition therapy is recommended according to the current American guidelines [8,9]. This mode of therapy affords the opportunity to achieve net protein anabolism and potentially avoid overfeeding-related complications in this at-risk population. Creative techniques, especially with enteral nutrition, may be necessary to achieve target caloric and protein goals. The close monitoring patients is mandatory with reference to increases in serum urea nitrogen concentrations in older patients or those with renal dysfunction, glycemic control for those with diabetes mellitus, insulin resistance, or stress-induced hyperglycemia, new-onset hypercapnia in ventilator-dependent patients, elevated serum triacylglycerols in those receiving intravenous lipid emulsion, as well as laboratory and clinical markers that are reflective of worsening adiposity-related and stress-induced metabolic perturbations.

However, most studies in support of this therapy have demonstrated equivocal outcomes to eucaloric or hypercaloric nutrition therapy with the exception of one small retrospective study that indicated superiority in clinical outcomes [58]. One randomized controlled trial indicated a lesser requirement for insulin therapy [28]; however, this study was conducted before the advantages of glycemic control in critically ill patients were known [30] and higher target blood glucose concentrations were allowed in that study than in current practice. A large, prospective, randomized, controlled trial is warranted to ascertain whether hypocaloric, high-protein nutrition therapy is superior than eucaloric or hypercaloric feeding with respect to clinical outcomes and avoidance of overfeeding complications.

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