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When a Calorie Isn't Just a Calorie: A Revised Look at Nutrition in Critically Ill Patients with Sepsis and Acute Kidney Injury

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Abstract

Purpose of review: To discuss how nutritional management could be optimized to promote protective metabolism in sepsis and associated acute kidney injury.

Recent findings: Recent evidence suggests that sepsis is a metabolically distinct critical illness and that certain metabolic alterations, such as activation of fasting metabolism, may be protective in bacterial sepsis. These findings may explain the lack of survival benefit in recent randomized controlled trials of nutrition therapy for critical illness. These trials are limited by cohort heterogeneity, combining both septic and non-septic critical illness, and the use of inaccurate caloric estimates to determine energy requirements. These energy estimates are also unable to provide information on specific substrate preferences or the capacity for substrate utilization. As a result, high protein feeding beyond the capacity for protein synthesis could cause harm in septic patients. Excess glucose and insulin exposures suppress fatty acid oxidation, ketogenesis and autophagy, of which emerging evidence suggest are protective against sepsis associated organ damage such as acute kidney injury.

Summary: Distinguishing pathogenic and protective sepsis-related metabolic changes are critical to enhancing and individualizing nutrition management for critically ill patients.

Keywords

Critical illness; nutrition; sepsis; metabolism; acute kidney injury

Introduction

The most recent clinical consensus defines sepsis as life-threatening organ dysfunction owing to dysregulated host response to infection [1]. Sepsis remains a global health problem with over 31 million sepsis cases and 5 million deaths worldwide annually [2]. In the United States, sepsis accounts for 50% of in-hospital deaths even though it accounts for only

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10% of hospitalizations [3]. Moreover, it remains the most expensive hospital diagnosis [4]. Despite broad-spectrum antibiotics and life-supporting technologies, therapeutics to improve sepsis outcomes remain limited. We have long appreciated the hallmark characteristics of metabolic derangements in sepsis, including hyperglycemia resulting from gluconeogenesis and insulin resistance, hyperlipidemia from lipolysis, and enhanced protein catabolism [5]. While many of these metabolic derangements have traditionally been viewed as entirely pathologic, emerging evidence suggests a complex relationship between host defense and metabolism. Host defense consists of both disease resistance, which involves pathogen clearance, and disease tolerance, in which physiologic responses are activated to limit tissue damage [6-8]. Some metabolic alterations resulting from the immune response to an infection may reflect protective defense mechanisms involved in disease tolerance. Thus, current attempts to reverse metabolic derangements associated with sepsis may be counterproductive. For example, the loss of muscle mass from increased protein catabolism is associated with poor outcomes in sepsis [9]. However, the proteolytic response in sepsis could be an essential adaptive response to fuel the liver's synthesis of acute phase proteins [10], many of which are important in host defense. Similarly, changes in glucose metabolism are considered pathologic given the association of hyperglycemia with increased mortality in critical illness [11]. However, it has been proposed that the purpose of this change in glucose metabolism is to redirect glucose utilization, including fueling the immune system for the initial antimicrobial response [12]. While lipolysis and the resulting hyperlipidemia could be considered maladaptive [13-16], there is evidence that lipoproteins are capable of binding and neutralizing endotoxin [17]. Moreover, the mobilized lipid substrates could be used as fuel for fatty acid oxidation (FAO) [5]. Many of our current approaches to minimize the consequences of these metabolic changes are indirect rather than targeting the root cause. Moreover, correction of abnormal clinical metabolic metrics by any means possible, without full consideration of the potential adverse consequences, could lead to harm. With a better understanding of metabolic disease tolerance pathways, we may need to revise our current management of septic patients to limit organ damage such as acute kidney injury (AKI) and optimize survival.

Clinical trials for nutritional therapy in critical illness: Interpretations and limitations

The provision of nutrition is a major factor contributing to the metabolic state of a septic patient. Many recent clinical trials have addressed timing, route, and caloric content of nutritional therapy in critically ill patients without any significant effect on survival (Table). The EDEN and PermiT trials showed that low calorie, trophic feeds are safe, but do not improve survival [18, 19]. Alternatively, the TARGET trial suggests feeding more also does not improve outcomes [20]. The CALORIES and NUTRIREA-2 trials showed that the route of early feeding, enteral versus parenteral, did not alter survival [21, 22]. However, the occurrence of severe gastrointestinal adverse effects observed in NUTRIREA-2 led to concerns about excessive enteral feeding in mechanically ventilated patients on vasopressors. Finally, if patients cannot tolerate enteral feeds, the EPaniC trial suggests the addition of parenteral feeds could cause harm if given too early [23]. Overall, the lack of mortality benefit in all these trials has left significant equipoise on how best to deliver nutritional therapy to critically ill patients.

There are several limitations of these trials precluding applicability to critically ill septic patients. First, energy expenditure (EE) and therefore presumed energy requirements were estimated, not measured. It is well established that equations using static anthropometric measurements such as height and weight to estimate EE are inaccurate in critically ill patients, including those with AKI [24-27]. EE is also known to be dynamic, classically described by Cuthbertson in 1942 as the Ebb and Flow energy phases of hemorrhagic shock [28], and variable depending on the presence and severity of sepsis [29]. Thus, multiple guidelines recommend the use of indirect calorimetry, the gold standard, to measure EE in critically ill patients, including those with AKI, to guide nutritional therapy [30-32]. However, current commercially available indirect calorimeters can be inaccurate and are expensive, limiting routine clinical use. Fortunately, a new generation of indirect calorimeters that are more accurate and cost effective are in development [33]. As nonprotein calories are rarely differentiated, another layer of complexity is the calorie source, which is not fully addressed in these trials. Moreover, we do not know whether substrate preferences differ among various critical illnesses and across distinct phases of disease. Thus, differential metabolic downstream consequences of delivered carbohydrates and fat calories are not clear. Second, as is common in most intensive care unit (ICU) clinical trials, cohort heterogeneity is significant (Table, Figure 1A). These trials include a mix of medical, surgical, and neurological ICU patients. Another important clinical parameter with significant metabolic implications is the presence of sepsis. In fact, the composition of septic patients varied across these trials (Figure 1B). The causative pathogen was also not reported. The type of sepsis may be significant as preclinical studies suggest metabolic determinants of survival differ between bacterial and viral septicemia [34]. Thus, the imprecision of EE estimates without differentiating specific calories and the heterogeneity of critically ill patients included in these trials limit the clinical applicability to septic patients.

Protein catabolism: How to limit negative protein balance?

Critical illness is often associated with increased protein catabolism, leading to net negative nitrogen balance and loss of muscle mass, which are associated with increased mortality [9]. Pharmacologic and nutritional approaches have attempted to minimize negative nitrogen balance in critically ill patients with minimal benefit. For example, growth hormone is effective in improving nitrogen balance in critically ill patients, but at the cost of increasing mortality, incident sepsis, hyperglycemia and insulin use [35]. Nutritional approaches with high protein feeds which minimize negative nitrogen balance and improve outcomes have been supported by several observational studies [36]. However, in meta-analyses of randomized controlled trials (RCTs), high protein feeding in critically ill patients has not shown benefit [37, 38]. The association of higher protein intake with better outcomes seen in observational studies are limited by potential confounders. Patients who have a better prognosis will survive long enough to achieve nutritional targets and may receive more attention to optimize their nutritional support, introducing potential immortal time and indication bias. As some RCTs were confounded by differences in calorie intake, ongoing RCTs are addressing this to test the efficacy of higher protein nutrition in the critically ill at a fixed caloric intake [39, 40]. While these studies are ongoing, there remains the possibility that excess dietary protein could be harmful in critically ill patients.

In the example of continuous renal replacement therapy (CRRT), amino acid losses are known to occur [41, 42]. While iatrogenic losses should be replaced, the overall benefit of high protein feeds to minimize negative protein balance in AKI patients on CRRT is unclear. One RCT examined the use of indirect calorimetry to guide nutritional therapy and escalating dietary protein in AKI patients on CRRT [43]. While patients with increased nitrogen balance had improved survival and higher protein intake associated with increased nitrogen balance, higher protein intake itself was not associated with improved survival. This would suggest that the true relationship between nitrogen balance and survival involves another factor that minimizes negative nitrogen balance, such as resolution of the underlying critical illness. Similarly in a post-hoc analysis of the RENAL study, higher dietary protein intake was associated with higher rates of mortality [44, 45]. While the total dietary protein intake in both groups were relatively low, it is important to note that the higher protein intake group had significantly more septic patients. In other studies, the relative proportion of septic patients in a cohort appears to correlate with worse outcomes associated with higher dietary protein intake. For example, in small RCTs examining the effect of high protein intake on limiting muscle loss, studies with few (less than 10%) or unreported septic patients showed improved outcomes [46, 47], while one RCT with a high percentage (80%) of septic patients showed no effect [48]. Similarly, in an observational study in which half the cohort was septic, higher protein delivery was associated with increased muscle wasting [49]. In burn patients, sepsis is a primary determinant of protein catabolism [50]. Similarly, in amino acid balance studies, only patients who recovered from sepsis could achieve net protein synthesis with the provision of high protein nutrition [51, 52]. While critically ill non-septic and septic patients both have increased protein catabolism, the presence of sepsis appears to be a primary driver of outcomes and not nitrogen balance per se. Therefore, negative nitrogen balance is more likely to be reflective of the inflammatory state, similar to decreased serum visceral proteins such as albumin and pre-albumin, which are no longer recommended to guide nutritional therapy [53]. Thus, there is a critical need for methods to accurately measure protein utilization to guide nutritional delivery rather than targeting nitrogen balance.

Unfortunately, the inability to accurately measure the capacity for protein utilization is a major limitation in the clinical management of protein catabolism. Dietary protein requirements are derived from nitrogen balance estimates which compare urinary and other bodily losses against dietary intake. As nitrogen balance estimates have many limitations even for healthy individuals at equilibrium [54], use of these balance estimates to calculate dietary protein needs in critically ill septic patients is highly problematic. As there is no ability to store protein, dietary protein not utilized for synthesis must be catabolized and excreted primarily as urea. In sepsis, high, insuppressible rates of protein catabolism will result in increased urea production. As a result, calculation of estimated protein requirements with ongoing catabolism will continually increase with rising urinary urea excretion in the absence of appropriate protein utilization (Figure 2). In a pre-specified analysis of the EPaNIC trial, timing of parenteral nutrition did not change the incidence of AKI [55]. However, early parenteral nutrition slowed renal recovery potentially due to increased ureagenesis, which prolonged RRT. It was also estimated that 63% of extra nitrogen intake was net wasted in ureagenesis. Excess dietary protein, beyond the capacity

of utilization, is not only wasteful, it may also be deleterious. In fact, an unpublished subgroup analysis of an observational study suggesting a benefit of high protein intake in critically ill patients, the survival benefit was only observed in non-septic patients, while there was a trend toward increased mortality in septic patients [56, 57]. Osmotic urea diuresis, of which high dietary protein intake is a major cause, is a common cause of hypernatremia, which increases mortality in critically ill patients [58, 59]. High protein intake can also suppress autophagy [60], a regulated cellular mechanism that removes unfolded or misfolded proteins and damaged organelles, resulting in recycling of nutrients and cell survival. In preclinical sepsis models, autophagy has been shown to be protective, improving survival and organ function [61, 62]. This is particularly relevant in septic AKI, where inhibition of autophagy will increase septic AKI, while augmenting autophagy will limit septic kidney damage [63-67]. As a result, focusing on nitrogen balance alone to guide dietary protein interventions without considering capacity for utilization and potential adverse effects may inadvertently delay kidney recovery in critically ill patients.

Glucose versus fatty acid oxidation

It is well-appreciated that hyperglycemia associates with poor outcomes in critically ill patients [68]. However, glycemic control with insulin in the ICU remains controversial. Much of the controversy stems from the inability to reproduce the landmark Leuven I trial [69]. Subsequently, intensive glycemic control in the NICE-SUGAR multi-center RCT [70] led to increased mortality. While hypoglycemia has been cited to be the most likely cause of increased mortality, patients in the intensive control group also received more of both insulin and glucose. While hypoglycemic events are detrimental and are likely contributing to mortality, the exposure of excess insulin and glucose could also cause harm in sepsis.

Sepsis is associated with the development of anorexia, which is a highly conserved component of sickness behavior. Anorexia associated with sepsis contributes to activation of fasting metabolism. Normal fasting and starvation adaptation includes induction of FAO, gluconeogenesis, ketogenesis, and autophagy. Fasting metabolism is a primary mechanism by which caloric restriction and intermittent fasting promotes longevity and mitigates diseases [71-73]. It has been proposed that fasting metabolism is dysfunctional in sepsis [14, 74-77], and this abnormal fasting response is a driver of morbidity and mortality. While the quality, magnitude, and kinetics of the fasting metabolic pathways may differ in sepsis compared to normal fasting, many of these pathways are intact in septic patients and in preclinical models of sepsis [34, 78-80]. However, these pathways are suppressed by the provision of glucose even at hypocaloric levels [34, 81, 82]. For example, patients with sepsis exhibit a significant switch in global metabolism from glucose oxidation to FAO. This is evident in a lower respiratory quotient, reflective of increased lipid metabolism, seen in critically ill patients with sepsis compared to those without sepsis [83]. Moreover, septic patients have low glucose oxidation which cannot be induced with a hyperglycemic glucose clamp [81]. Instead, glucose infusion in septic patients will increase insulin levels while suppressing FAO [84] and ketogenesis [81, 82]. These data suggest FAO may be an adaptive response and the preferred metabolic state in sepsis.

Growing preclinical evidence supports a role for peroxisomal proliferator-activated receptor (PPARα) and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1α) as protective metabolic mediators in sepsis, limiting organ damage including AKI and improving survival [79, 85-92]. PPARα and PGC1α promote FAO, while PPARα also activates ketogenesis. Glucose and insulin could suppress metabolic pathways activated by PPARα and PGC1α. Glucose oxidation inhibits FAO through the metabolic intermediate, malonyl-CoA, and insulin promotes lipogenesis while inhibiting FAO and ketogenesis (Figure 3) [93]. Insulin will also suppress autophagy through activating mammalian target of rapamycin (mTOR), the main inhibitor of autophagy (Figure 3). One RCT of intensive glycemic control using insulin observed that increased insulin exposure associated with suppression of autophagy in critically ill patients [94]. A recent retrospective analysis of type 2 diabetic hospitalized patients with confirmed COVID-19 reported a significant relationship of insulin treatment with increased mortality, mechanical ventilation, and AKI [95]. Thus, the clinical consequences of suppressing FAO, ketogenesis and autophagy by insulin could be significant.

The possibility of glucose and insulin-regulated metabolism interfering with protective metabolic pathways in sepsis raises concerns of whether the way we feed and medicate septic patients could be counterproductive and potentially harmful. Commercially available enteral nutrition formulations are generally high in carbohydrate content. Many intravenous medications are delivered in dextrose containing solutions and parenteral nutrition is also formulated with significant glucose content. This high carbohydrate load ultimately will lead to increased obligate insulin requirements. In studies examining the effect of high versus low calorie or protein nutritional delivery on nitrogen balance in AKI patients on CRRT, the average glucose administered is close to 400 grams or more per day [96-98]. This amount of glucose will not only obligate more insulin, but it is also more than the carbohydrate oxidation capacity of AKI patients. One indirect calorimetry study found that AKI patients, both septic and non-septic, were not given enough lipid to support measured lipid oxidation rates, while carbohydrates were given more than actual glucose oxidation rates [99]. Thus, alternative approaches could include limiting the glycemic load or changing the delivery of feeds to allow for adequate periods of fasting capable of enhancing FAO, ketogenesis and autophagy [100].

Other metabolic considerations in sepsis:

Intermittent feeding.—Prior work has extensively examined the timing of feeding initiation in ICU patients, however an organized approach to comparing an intermittent versus continuous feeding protocol and by extension the importance of fasting periods in critically ill patients has yet to be undertaken. Several small non-inferiority RCTs reported favorably on clinical endpoints such as gastrointestinal distress and aspiration pneumonia for those receiving intermittent feeds compared to those continuously fed [100, 101]. However, the small sample sizes, lack of harder endpoints, inconsistent reporting on metabolic variables, and heterogeneity in feed and insulin administration protocols limit our ability to make broader conclusions about the effect of fasting duration on optimizing metabolism to survive critical illnesses such as sepsis. In contrast to outpatient intermittent fasting regimens using at least 16-18 hours of fasting [71], typical intermittent feeding protocols for critical

illness have at most 8 hours of fasting [102]. The optimal duration of the fasting state to promote the protective effects of autophagy, mitochondrial biogenesis, muscle protein synthesis and ketogenesis still lacks consensus, especially in septic patients. Van Dyck et al reported that 12 hours of fasting in critically ill patients was insufficient to alter autophagic marker expression levels in blood samples [103], suggesting a longer interval of fasting may be necessary. However, improved methods of measuring autophagy are needed as static blood expression levels may not be sufficient to determine autophagic flux or tissue specific autophagy [104]. Moreover, feed composition may still be a critical factor independent of fasting duration.

Underlying metabolic disease.—An additional complicating factor is the increasing prevalence of obesity, diabetes mellitus, sarcopenia, and cancer among critically ill patients. Common to these diseases and disorders is the presence of metabolic dysregulation. While the prognostic relationships are evident, the mechanistic effects of these underlying metabolic diseases on the acute phase of sepsis are not as clear. Moreover, metabolic inflexibility could render septic patients with these co-morbidities less likely to respond to metabolic and nutritional interventions [105, 106].

Immune system and the microbiome.—Immunometabolism is an important component of host defense [107-109]. Metabolic determinants of successful host response are complex with both infection- and immune cell type-specificity. It is unknown whether nutritional and metabolic interventions optimal for the immune system could conflict with peripheral organ metabolic response under stress conditions [108]. Nutritional exposures and medications, especially antibiotics, will also alter the gut microbiota and intestinal integrity, of which both impact inflammation and host responses to sepsis [110, 111]. Balance of these potentially conflicting metabolic demands needs to be considered when designing appropriate nutritional interventions.

Conclusion

Sepsis is a distinct metabolic entity compared to other critical illnesses. As such, the optimal metabolic and nutritional management will likely differ between septic and non-septic critically ill patients. Thus, it is critical to understand the metabolic determinants of host defense and disease tolerance. Growing evidence suggests that a switch towards a metabolic state favoring FAO, ketogenesis and autophagy may be protective in bacterial sepsis. In fact, several lines of preclinical evidence support FAO and autophagy as mechanisms to limit septic AKI. Development of bedside methods to accurately measure substrate preferences and capacity for utilization is needed to avoid excess nutrient delivery that could cause harm, while optimizing metabolic pathways that promote survival.

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Abbreviations:

AKI	acute kidney injury
CRRT	continuous renal replacement therapy
EE	energy expenditure
FAO	fatty acid oxidation
mTOR	mammalian target of rapamycin
NR	not reported
PGC1α	peroxisome proliferator-activated receptor gamma coactivator 1-alpha
PPARα	peroxisomal proliferator-activated receptor
RCTs	randomized controlled trials

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Key points:

1. Metabolic alterations associated with sepsis may represent protective defense mechanisms.
2. Without fully understanding sepsis pathophysiology, iatrogenic interventions meant to correct abnormal clinical parameters such as hyperglycemia and negative nitrogen balance could lead to harm.
3. Similar to decreased visceral proteins, negative nitrogen balance likely reflects ongoing inflammation and would not serve as an appropriate target for nutrition therapy.
4. Excess glucose and insulin exposure could lead to inhibition of fatty acid oxidation and autophagy, metabolic pathways that support survival and limit AKI in preclinical sepsis models.
5. Development of bedside methods to accurately measure substrate preferences and capacity for utilization is critically needed.

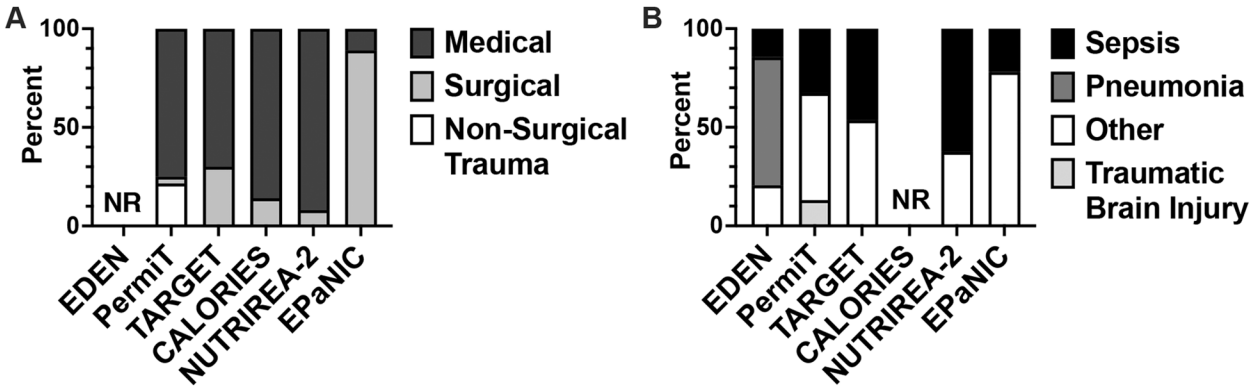

Figure 1. Cohort heterogeneity in intensive care unit nutrition therapy clinical trials

A. Study population by intensive care unit setting by percentage. B. Study population by type of critical illness by percentage. NR, not reported.

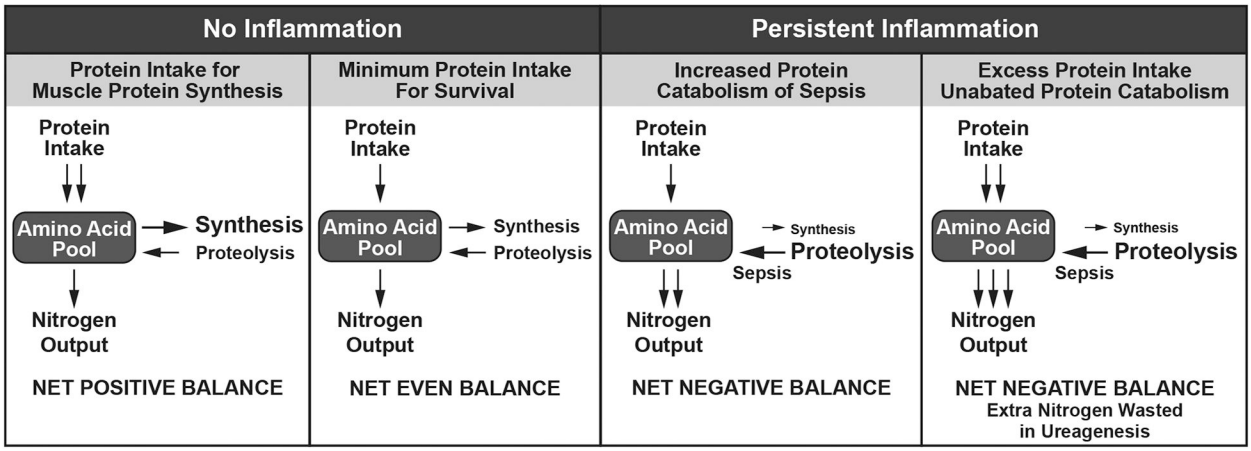

Figure 2. Nitrogen balance in health and disease.

In the absence of inflammation, positive nitrogen balance and muscle protein synthesis are possible. Excess dietary protein in the presence of ongoing inflammation due to diseases such as sepsis, will lead to wasted nitrogen in ureagenesis and could cause harm.

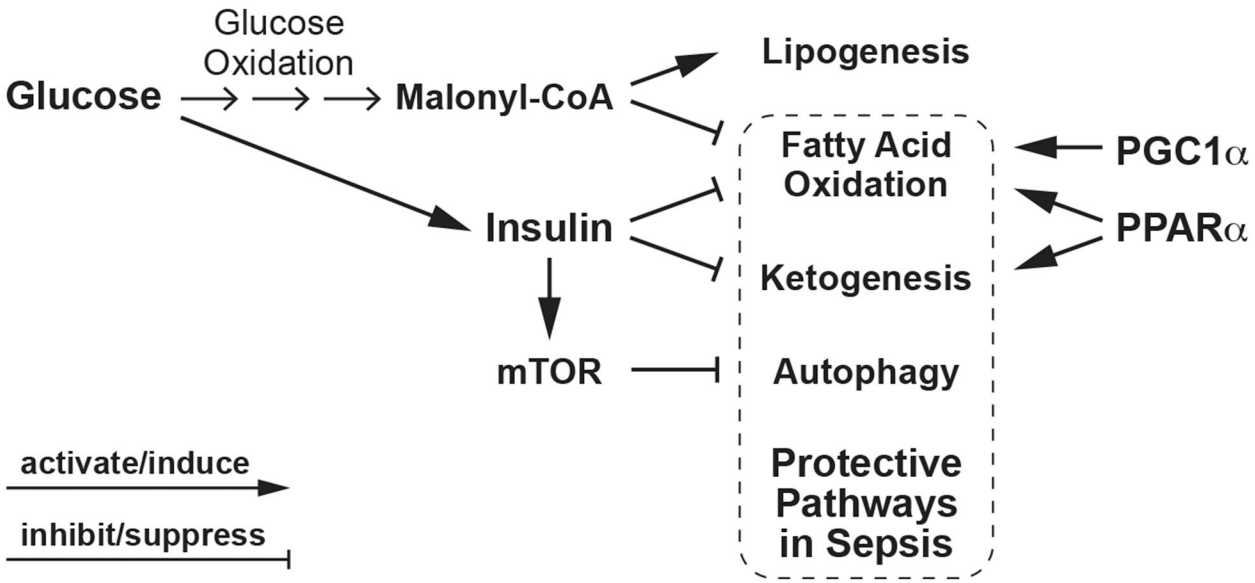

Figure 3. Metabolic effects of glucose and insulin.

Glucose oxidation promotes lipogenesis and inhibits fatty acid oxidation. In response to elevated blood glucose levels, secreted insulin regulates glucose storage while inhibiting fatty acid oxidation, ketogenesis, and autophagy through the activation of mTOR, a strong inhibitor of autophagy. PPARα and PGC1α promote fatty acid oxidation, while PPARα activates both fatty acid oxidation and ketogenesis. Fatty acid oxidation, ketogenesis, and autophagy have all been proposed as protective pathways in sepsis. Thus, excess glucose or carbohydrate nutritional delivery and the resulting obligate insulin requirements could lead to suppression of these protective metabolic pathways.

Table 1

Recent Intensive Care Unit Nutrition Therapy Clinical Trials

Author Study Year	Study population	Study regimen/Intervention		Primary Outcomes	Secondary Outcomes
Rice (EDEN) 2012 [18]	Mechanically ventilated patients within 48 hours of acute lung injury	Trophic[1]	Full[2]	No difference in ventilator free days	Full feeding group with increased GI adverse effects (vomiting, residuals) and increased insulin use.
Arabi (PermiT) 2015 [19]	Patients fed enterally within 48 hours of ICU admission	Permissive underfeeding[3]	Standard feeding[4]	No difference in 90-day all-cause mortality	Standard feeding group with more incident RRT, higher blood glucose, and increased insulin use.
Chapman (TARGET) 2018 [20]	Mechanically ventilated ICU patients	Energy dense enteral[5]	Routine enteral[6]	No difference in 90-day all-cause mortality	Energy dense group had increased GI adverse effects (vomiting, residuals) and increased insulin use.
Harvey (CALORIES) 2014 [21]	ICU patients requiring nutritional support[7]	Enteral[8]	Parenteral[8]	No difference in 30-day all-cause mortality	Enteral group had increased GI adverse effects (vomiting) and increased rates of hypoglycemia.
Reignier (NUTRIREA-2) 2018 [22]	Mechanically ventilated ICU patients requiring vasoactive therapy and nutritional support	Enteral[9]	Parenteral[9]	No difference in 28-day all-cause mortality	Enteral group had increased GI adverse effects (vomiting, diarrhea, bowel ischemia, and acute colonic pseudo-obstruction), increased rates of hypoglycemia, and less insulin use.
Casaer (EPanIC) 2011 [23]	Nutritionally at risk ICU patients (not meeting caloric goals with enteral nutrition)	Early PN initiation[10]	Late PN initiation initiated on day 8[10,11]	Early PN had increased ICU length of stay.	Early PN group had increased ICU infections, longer hospital length of stay, and longer duration of MV and RRT.

[1] 20 kcal/h

[2] 25-30 kcal/kg/d of nonprotein calories and 1.2-1.6 g/kg/d of protein

[3] 40-60% estimated caloric needs

[4] 70-100% estimated caloric needs

[5] Enteral feed with 1.5kcal/mL at a target rate of 1 ml/kg calculated ideal body weight/hr.

[6] Enteral feed with 1.0 kcal/mL at a target rate of 1 ml/kg calculated ideal body weight/hr.

[7] Cohort included 83% mechanically ventilated and 83% requiring vasoactive agents.

[8] Energy target of 25 kcal/kg of actual body weight/d.

[9] 20-25 kcal/kg of actual body weight/d first 7 days, then 25-30 kcal/kg of actual body weight/d from day 8 to extubation.

[10] Caloric goal included protein energy and were based on corrected ideal body weight, age, and sex.

[11] If enteral nutrition was insufficient after 7 days in the ICU, parenteral nutrition was initiated on day 8 to reach the caloric goal.

Intensive Care Unit (ICU), Mechanical ventilation (MV), Gastrointestinal (GI), Renal Replacement Therapy (RRT), Parenteral Nutrition (PN)