Role of ketones, ketogenic diets and intermittent fasting in ICU

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Word count (max 2500): 2060

Structured abstract (max 200 words; max 3-5 keywords)

Purpose of review:

To summarize the clinical evidence for beneficial effects of ketones, ketogenic diets and intermittent fasting in critical illness, and to review potential mechanisms behind such effects.

Recent findings:

Recent evidence demonstrates that activation of a metabolic fasting response may be beneficial to recover from critical insults. Potential protective mechanisms are, among others, activation of ketogenesis and of damage removal by autophagy. Novel feeding strategies, including ketone supplements, ketogenic diets and intermittent fasting regimens, can activate these pathways – at least partially– in critically ill patients. Randomized controlled trials (RCTs) studying these novel feeding strategies as compared to standard care, are scarce and have not shown consistent benefit. Yet, all RCTs were small and underpowered for clinical endpoints. Moreover, in intermittent fasting studies, the duration of the fasting interval may have been too short to develop a sustained metabolic fasting response.

Summary:

These findings open perspectives for the further development of fasting-mimicking diets. Ultimately, clinical benefit should be confirmed by RCTs that are adequately powered for clinically relevant, patient-centered endpoints.

Keywords: ketones, autophagy, intermittent fasting, nutrition, critical illness

Introduction

Although numerous observational studies have associated accumulation of a caloric and protein deficit with adverse outcome of critical illness, large randomized controlled trials (RCTs) have not confirmed the hypothesized benefit of early enhanced nutritional support to intensive care unit (ICU) patients, and several RCTs even found potential harm [1-5]. Although some experts have attributed the absence of benefit to suboptimal dosing of individual macronutrients, an alternative emerging explanation is that the underlying assumption may be invalid [6,7]. Indeed, for decades, artificial feeding has been administered in an effort to counteract critical illness-associated catabolism and associated muscle wasting [6]. This traditional viewpoint assumes that feeding can attenuate loss of lean body mass in critical illness, and that the fasting response is intrinsically negative and mainly meant to preserve substrate availability to vital organs in times of scarcity [6]. However, recent evidence has shown that catabolism is feeding-resistant in critically ill states and that feeding may pose an additional metabolic burden, especially in the acute phase of illness [8-10]. Moreover, increasing evidence has shown that the effects of the well-orchestrated fasting response go far beyond preserving energy supply to vital organs and tissues. Indeed, fasting powerfully activates cell-protective and cellular repair pathways, including autophagy, mitochondrial biogenesis, and antioxidant defenses, which may promote resilience to cellular stress [11**]. In this regard, activation of fasting responses through caloric restriction and fasting-mimicking diets has shown to prolong life span and to protect against age-related diseases in animal models [12]. Also in humans, fasting-mimicking diets were found to attenuate risk factors for cardiovascular disease [11**]. Collectively, this recent evidence suggests that intermittent activation of the fasting response may be important for maintaining homeostasis.

In this review, we will summarize the mechanisms whereby the fasting response could be beneficial in critical illness, followed by the clinical evidence and future perspectives.

Mechanisms by which fasting can be beneficial in critical illness

In the last decade, several fasting-activated mechanisms have emerged as potentially protective pathways in critically ill states, including activated ketogenesis and autophagy.

Activated ketogenesis

In healthy individuals, fasting induces a progressive switch from carbohydrate to lipid metabolism, with activation of ketogenesis [13,14]. With prolonged fasting duration, ketones have increasing contribution as alternative energy source. Ketones are more energy-efficient than glucose and have shown to increase physical endurance in athletes [13,15]. Apart from having a role as energy substrate, ketones also exert multiple signaling functions [13]. The downstream pathways affected include activation of oxidant defenses, mitochondrial biogenesis, autophagy, and anti-inflammatory pathways, which are all presumed to be important in recovery from critical illness [13,16]. In line with this, ketone supplementation enhanced muscle regeneration and force in a septic rodent model, which appeared to be explained by its effects as signaling molecule [17]. Conversely, hepatocyte-specific deletion of peroxisome proliferator-activated receptor α impaired activation of ketogenesis and decreased survival in septic mice [18]. Animal studies in brain-injured models also have found protective effects of ketone supplementation or a ketogenic diet, with some studies showing improved mitochondrial function and reduced oxidant stress [19].

Observational studies in critically ill patients support a protective role of enhancing ketone availability. Indeed, as compared to providing early parenteral nutrition (PN), withholding PN in the first week after ICU admission activated ketogenesis in critically ill children up to the millimolar range, which statistically mediated part of its beneficial outcome effect in the Pediatric Enteral versus Parenteral Nutrition in Critical Illness (PEPaNIC)-RCT [20**]. Also in critically ill adults, withholding early PN significantly increased ketogenesis in a substudy of the EPaNIC-RCT, yet to a lower extent than in children and without an association with outcome [21*]. These findings correspond to observations in healthy children, who also have more pronounced fasting-induced ketogenesis than healthy adults [22]. Altogether, although speculative, this could explain why critically ill children had an apparent greater outcome benefit through withholding early PN than adults. Important to note, however, is that all patients in the adult RCT received tight glucose control with insulin therapy, unlike in the pediatric RCT [20**,21*]. The impact of glucose control with insulin therapy on ketogenesis in critically ill patients remains speculative. Whereas insulin is a powerful suppressor of ketogenesis, critical illness-associated hepatic insulin resistance is severe and difficult to overcome with insulin therapy, and stress hyperglycemia by itself may also suppress ketogenesis [23,24].

Activated autophagy

A second potentially important protective mechanism activated by fasting is macroautophagy, hereafter referred to as autophagy. Autophagy is a process whereby cytoplasmic content is engulfed by autophagosomic vesicles that subsequently fuse with lysosomes for degradation. Autophagy serves important housekeeping functions, as illustrated by the severe phenotypes that occur when autophagy is selectively knocked out in mice [25**]. Importantly, autophagy is the only cellular process able to degrade macromolecular damage, including damaged or

dysfunctional organelles and potentially toxic protein aggregates [26]. Autophagy also has important roles in clearance of intracellular microorganisms. Given its important housekeeping functions, dysregulation of autophagy has been implicated in various human diseases [25**,26]. Apart from activation by a variety of stress signals, autophagy is powerfully activated by fasting [25**,26]. Indeed, upon nutrient deprivation, metabolic sensors activate the autophagic machinery to provide endogenous substrate [25**]. Although ketones may promote fasting-induced autophagy, several ubiquitous ketone-independent triggers are probably more important to initiate autophagy during fasting [25**,27].

In the last decade, several mechanistic studies have identified a crucial role of autophagy in mediating recovery from critical illness. First, a landmark study in 2011 revealed hallmarks of insufficient autophagy in liver and muscle of critically ill patients who had died in the ICU [28]. Since then, the causal link between activated autophagy and improved outcome from critical illness has been confirmed by numerous animal studies. Indeed, in different models of critical illness (burn injury, sepsis, toxin-mediated and ischemia reperfusion injury), pharmacological or genetical activation of autophagy improved outcome, whereas inactivation had the opposite effect [26,29,30]. Although this opens perspectives for pharmacological autophagy activation in critically ill patients, there are no specific inducers available [31]. Existing drugs with autophagy-activating potential have important other pharmacological effects that may be unwanted [32]. Importantly, autophagy can also be affected by modulating nutrition in critical illness, which may be a more straightforward approach [32]. Indeed, a secondary analysis of the PermiT-RCT revealed differential gene expression in peripheral white blood cells of patients randomized to permissive underfeeding (40 – 60% of calculated caloric requirements) versus standard feeding, suggestive of autophagy activation by permissive underfeeding [33]. Moreover, autophagy activation has emerged as one potential mechanism explaining why withholding early PN was found to be beneficial. Indeed, in an animal model of critical illness,

relative macronutrient restriction activated autophagy in liver and muscle as compared to early PN, which coincided with less organ damage [34]. Likewise, in a substudy of the EPaNIC-RCT, withholding early PN activated autophagy in muscle of adult critically ill patients, which associated with less weakness upon awakening in ICU [9].

Other mechanisms

Apart from stimulating ketogenesis and autophagy, fasting also activates other cellular recovery pathways, including activation of mitochondrial biogenesis, antioxidant defenses, and DNA repair, which may lead to a greater resilience to cellular stress [11**]. Feeding strategies that alternate fasting and feeding intervals may be protective through additional mechanisms, including a better preservation of circadian rhythm, improved insulin sensitivity and improved muscle protein synthesis through avoidance of the muscle-full effect [35*,36*]. Finally, feeding strategies that temporarily withhold enteral nutrition could be beneficial through intermittent restoration of gastric acidity, which could reduce bacterial colonization and the risk of ventilator-associated pneumonia [37]. However, a small RCT did not find a difference in respiratory tract colonization and incidence of pneumonia between intermittent versus continuous feeding, despite a temporarily lower gastric pH in the intermittently fed group [37]. Moreover, 2 recent RCTs have not shown a difference in pneumonia incidence between early enteral nutrition and isocaloric PN, although gastric pH was not measured and there may have been confounding by stress ulcer prophylaxis [38,39].

Translation into clinical practice

Although the fasting response may activate potentially important recovery processes in critical illness, prolonged fasting ultimately comes at the price of losing lean body mass [40]. However, increasing evidence suggests that the beneficial pathways induced by fasting can be activated by modified nutritional strategies, among which are ketone supplementation, ketogenic diets and intermittent fasting [11**,12]. These novel feeding strategies may allow to continue feeding in patients while preserving fasting responses. Clinical superiority remains to be demonstrated, however.

Ketone supplementation and ketogenic diets

In clinical practice, exploiting the potential benefit of ketones could be done by studying the impact of ketone supplementation or of ketogenic diets with high fat and low carbohydrate content. Although animal studies have shown benefit of ketogenic diets or ketone supplementation in models of brain injury and sepsis, clinical evidence remains scarce [17,19]. Indeed, existing RCTs in patients with traumatic brain injury and sepsis only included a limited number of patients to examine metabolic changes, and were not powered for clinical endpoints [41,42]. These RCTs found suppression of gluconeogenesis and improved glucose control by ketone supplementation and a ketogenic diet, respectively [41,42]. In clinical practice, ketogenic diets have been used for decades to successfully treat patients with therapy-resistant status epilepticus, although solid RCT evidence confirming efficacy is limited [43]. In critical illness, successful application of a ketogenic diet might be particularly challenging due to interfering co-administration of carbohydrate- or alcohol-containing drugs [44]. Future research should examine the efficacy and safety of ketone supplementation and ketogenic diets in critically ill patients through adequately powered RCTs.

Intermittent fasting

In aging research, numerous animal studies have shown that the benefits of caloric restriction and fasting can be replicated through so-called fasting-mimicking diets [11**,12]. The common ground of these diets is that feeding intervals are alternated with fasting intervals, although there is considerable variation in the studied timing and duration of the fasting episodes [12]. In critical illness, however, it has been questioned if patients can mount a full metabolic fasting response, and how long the fasting interval should last to obtain such response [45,46]. In a pilot crossover RCT, Van Dyck et al. investigated whether a fasting interval of 12 hours is sufficient to generate a metabolic fasting response [47**]. The study showed a clear fasting response after 12 hours interruption of artificial feeding, with increases in circulating ketones and bilirubin, and decreased insulin requirements and serum insulin-like growth factor I concentrations. Importantly, ketone concentrations already increased after 4 hours of fasting. In contrast, markers of autophagy were not affected in circulating white blood cells. Yet, it remains unclear how to interpret this finding, since white blood cells are not a validated readout for the activation status of autophagy at the level of other tissues [47**].

Several RCTs have investigated whether intermittent feeding is clinically superior to continuous feeding for critically ill patients [48**,49*]. Altogether, these RCTs failed to demonstrate consistent clinical benefit from intermittent feeding [48**,49*]. However, all RCTs were relatively small (including 18-164 patients) and were likely underpowered to detect or exclude a meaningful benefit. Moreover, the study design considerably varied among studies, and most RCTs focused on feeding intolerance and/or pulmonary aspiration [48**,49*]. Whereas some RCTs found more gastrointestinal intolerance by intermittent feeding, other RCTs were neutral and 2 RCTs suggested potential benefit with regard to feeding intolerance and/or the risk of aspiration pneumonia [48**]. One multicenter RCT did not detect a benefit

of intermittent feeding with regard to ultrasound-assessed muscle loss in patients expected to require a prolonged ICU stay [49*]. Yet, apart from measurement inaccuracies, primary outcome data were missing in approximately half of patients, which may have induced bias [50]. Besides a lack of power, the fasting interval in all RCTs on intermittent feeding was relatively short (maximum 6 hours), which may have been insufficient to induce a sustained fasting response and activate its associated cellular repair pathways [35*]. Future studies should investigate the optimal duration of the fasting interval for critically ill patients, if any, and validate this in an RCT that is adequately powered for clinical endpoints [51].

Conclusion

Increasing evidence demonstrates that the fasting response induces cell-protective and recovery-enhancing pathways, among which are activated ketogenesis and autophagy. Novel feeding strategies, including ketone supplementation, ketogenic diets, and intermittent fasting, can activate these protective pathways at least partially in critical illness, while avoiding prolonged starvation. Whether application of such novel feeding strategies is clinically beneficial, remains to be studied in large RCTs that are adequately powered for clinical endpoints.

Key points (3-5 key bullet points; 1 sentence per bullet point)

1. Increasing evidence suggests that regular activation of a fasting response is beneficial for critically ill patients, to promote resilience to cellular stress and enhance cellular recovery.
2. The potentially protective pathways activated by fasting in critical illness include activation of ketogenesis and stimulation of damage removal by autophagy.
3. Novel feeding strategies, including ketone supplementation, ketogenic diets and intermittent fasting, may allow to activate beneficial fasting responses in critically ill patients while avoiding prolonged starvation.
4. Although animal studies in critically ill models have found benefit by increased ketone availability and intermittent fasting, the clinical efficacy remains to be studied in large randomized controlled trials.

Acknowledgements

Acknowledgements

None

Financial support and sponsorship

JG and MPC receive a postdoctoral research fellowship from the University Hospitals Leuven and the Research Foundation – Flanders, respectively, and C2 project funding from KU Leuven (C24/17/070)). JG and GVdB receive a research grant from the Research Foundation – Flanders (T003617N). GVdB holds an ERC Advanced grant (AdvG-2017-785809) from the Horizon 2020 Program of the EU and receives long-term structural funding from the Methusalem Program of the Flemish Government (METH/14/06).

Conflicts of interest

GVdB and LL are inventors on a patent related to the content of the manuscript (PCT/EP2017/081394).

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