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## Review Article

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# Circadian rhythms, feeding patterns and metabolic regulation: implications for critical care

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**Abstract**

Endogenous biological rhythms synchronise human physiology with daily cycles of light-dark, wake-sleep and feeding-fasting. Proper circadian alignment is crucial for physiological function, reflected in the rhythmic expression of molecular clock genes in various tissues, especially in skeletal muscle. Circadian disruption, such as misaligned feeding, dysregulates metabolism and increases the risk of metabolic disorders like type 2 diabetes. Such disturbances are common in critically ill patients, especially those who rely on enteral nutrition. Whilst continuous provision of enteral nutrition is currently the most common practice in critical care, this is largely dictated by convenience rather than evidence. Conversely, some findings indicate that intermittent provision of enteral nutrition aligned with daylight may better support physiological functions and improve clinical/metabolic outcomes. However, there is a critical need for studies of skeletal muscle responses to acutely divergent feeding patterns, in addition to complementary translational research to map tissue-level physiology to whole-body and clinical outcomes.

Endogenous biological rhythms synchronise human physiology with the daily cycles of light and dark, wakefulness and sleep, as well as feeding and fasting. This synchronisation typically aligns human behaviours such as wakefulness, activity and feeding with the daylight hours – while sleep, rest and fasting are aligned with nighttime[1–6].

In the context of these daily fluctuations in physiological regulation, temporal eating patterns (i.e. chrononutrition) are a key consideration for metabolic health, such that asynchrony between these states (e.g. through nocturnal eating patterns) can misalign the circadian timing system, leading to impairment of physiological function, increasing the risk for developing chronic metabolic disorders[3,7–9]. This is a topic of growing interest in the context of critical care whereby the environmental conditions within the intensive care unit (ICU), drastically differ from free-living conditions. In particular, the current default approach of continuous provision of nutrients to patients unable to feed themselves may further exacerbate circadian misalignment in critically ill patients thereby impacting recovery and long-term outcomes[10]. Among critically ill patients who receive enteral nutrition, approximately 33% develop insulin resistance, which might be explained by endocrine disruption and/or skeletal muscle wastage due to inappropriate or misaligned enteral nutrition delivery patterns[11,12,13]. Remarkably, this practice is largely driven by convenience and ease of administration, rather than being based on a robust understanding of its impact on patients' circadian rhythms and recovery.

The aim of this review is to summarise the current understanding of the importance of biological rhythmicity and feeding patterns in metabolic regulation, explore the existing evidence supporting an intermittent pattern of enteral feeding in a critical care setting, and highlight the potential directions for future research to address the current gaps in our understanding. In doing so the review aims to set the stage for future work that can inform and optimise nutritional strategies in critical care settings.

### *Biological rhythms and their significance in muscle metabolism*

Skeletal muscle, in particular, is a robustly rhythmic tissue, which may underpin the coordinated disposal, degradation and synthesis of metabolic substrates across the day[14–19]. Skeletal muscle is responsible for a significant proportion (~40–85 %) of dietary glucose and lipid disposal and is an important reservoir of amino acids stored as protein[20–24]. Previous work has revealed diurnal rhythmicity in ~1000 genes in skeletal muscle including those related to glucose and lipid metabolism, as well as protein turnover[15,17,25]. Lipidomic analysis within the same cohort identified diurnal rhythms in lipid metabolites particularly major membrane-lipid species such as the sphingolipids that are involved in insulin signalling and insulin resistance[14]. Similarly,

genes related to autophagy – a vital component of the skeletal muscle adaptive response to variable nutrient supply[26,27] – also exhibit a diurnal rhythm[17].

The relative importance of such rhythms in skeletal muscle for health and function is apparent from studies utilising circadian disruption either through misalignment of environmental cues or through experimental in vitro and in vivo (i.e. animal models) disruption of the endogenous clock. Disturbance of typical rhythms in skeletal muscle compromises the lipidome and can reduce the uptake/transport, utilisation and non-oxidative storage of glucose (i.e. glycogen synthesis), thereby reducing insulin sensitivity in human skeletal muscle[17,28–33]. These effects heighten the risk of type 2 diabetes (T2D), which itself is characterised by blunted circadian oscillations, collectively suggesting that circadian disruption is a defining feature of the insulin-resistant state[34,35]. Loss of key clock proteins, such as *Bmal1*, leads to an accelerated sarcopenic phenotype with age in mice[36], and impairs various aspects essential for proper muscle performance, including sarcomeric structure, mitochondrial morphology and muscle contractile activities[37]. Collectively, this evidence highlights the importance of rhythmicity within skeletal muscle for both metabolic health and function.

## Clinical implications of skeletal muscle rhythms for critically ill patients

Maintaining typical circadian rhythmicity of skeletal muscle is especially important for critically ill individuals. Despite a worldwide increase in survival rates of critically ill patients, long-term outcomes for those who do survive remain poor. A significant proportion experience chronic impairment in metabolism, sleep, physical function and cognitive and psychological health[38]. These adverse outcomes can be attributed to a myriad of factors, such as muscle disuse and inflammation stemming from injury or illness, among others[11–13]. While these factors could theoretically vary based on the specific conditions and circumstances of each patient, one common element that could markedly impact all critically ill patients is circadian disruption due to the stark contrast between typical daily life and the 24-h schedule of a working ICU environment[10,39–41]. Consequently, understanding and addressing circadian disruption could be a key aspect of improving outcomes in critically ill patients. One such practically feasible strategy for targeting circadian disruption is through the appropriate provision (e.g. amount and timing) of nutrition to critically ill patients.

## Enteral feeding patterns in critically ill patients

Annually, critical care units in the UK admit approximately 200,000 patients[42] and it's estimated that between 30 and 50% of these patients are already malnourished at the time of their admission[43]. Approximately half of admitted critically ill patients will be fed enterally, providing vital support for various conditions (e.g. palliative, post-surgical and intensive care)[44], because they are unable to feed themselves for a prolonged period[45]. However, ~33% of enterally fed patients develop insulin resistance and a larger portion experience substantial muscle atrophy[12,46,47]. Both of these could be explained, in part, by inappropriate delivery of enteral nutrition – which may exacerbate circadian disruption, further impairing metabolism at the tissue level of skeletal muscle. There is evidently a need to consider the implications of enteral feeding patterns in critically ill patients to maintain daily rhythmicity and prevent further deterioration of metabolism.

The default and most prevalent pattern worldwide is to deliver nutrients continuously, yet this decision is based on convenience, not evidence. Recent systematic reviews consistently call for research into whether an intermittent feeding pattern may be superior[48–50]. A number of studies have explored the effects of intermittent feeding in the Intensive Care Unit (ICU). These studies have not been successful in showing improvements in morbidity or mortality[41,51,52]. However, it is worth noting that intermittent feeding protocols often still include nighttime feeding or lack a sufficiently long fasting period, factors that could potentially undermine the potential benefits of this approach[52–58].

Continuous feeding presents practical problems, with unscheduled interruptions for clinical procedures such that nutritional targets are unmet. Moreover, a permanently postprandial (fed) state extending throughout most, or all of the sleeping phase is unlikely to be optimal for physiological function or circadian alignment. By contrast, regular bolus feedings specific to the daylight/waking phase are more aligned both with our natural eating patterns and with entrained biological rhythms in clinically relevant processes such as metabolic regulation/flexibility, protein turnover and autophagy[41,51,59,60]. For instance, intermittent protein ingestion more effectively stimulates muscle protein synthesis than a continuous amino acid supply, which is an important outcome in critically ill patients to minimise the risk of muscle wastage[61–63]. Normal meal intake results in the pulsatile release of insulin and ghrelin[64], which is preserved with intermittent enteral feeding but lost with continuous feeding. Given that insulin is a potent modulator of clock gene and/or protein expression in multiple tissues, this pulsatile release may be necessary for maintaining rhythmicity in skeletal muscle[65,66,67,68,69]. Interestingly, under controlled conditions the diurnal rhythm of skeletal muscle genes related to glucose, lipid and protein metabolism are temporally related to the diurnal profile of insulin, highlighting the potential for feeding patterns to modulate and entrain skeletal muscle rhythmicity[25]. Notably, shortening of the eating window through time-restricted feeding has been shown to increase the amplitude of oscillating muscle transcripts[70]. However, neither the acute response (i.e. 24-h) nor adaptation time of skeletal muscle to novel feeding patterns has been established[41,71].

Nonetheless, intermittent provision of enteral nutrition attenuates the progressive rise in plasma leptin and insulinemia seen with continuous feeding during bed res[t][47] potentially enhancing splanchnic blood flow, and improve gastrointestinal tolerance of enteral nutrition while influencing skeletal muscle autophagy[72]. While intermittent enteral nutrition may increase the risk of diarrhoea, it can reduce the incidence of constipation, without affecting other gastrointestinal outcomes[73]. From a practical perspective, intermittent feeding offers several advantages. It imposes less limitation on patient mobility and necessitates fewer pauses for procedures or tests. It may also help achieve enteral calorie targets faster than continuous feeding in line with international guidelines emphasising the importance of providing early adequate enteral nutrition for critically ill patients[52–54,74–76].

In theory, intermittent feedings could sustain organ stress resistance and promote overall resilience, thus improving patient response to treatment and recovery from illness[51,59,60]. It is thus remarkable that the links between nutrient timing, chronobiological strain and human health outcomes remain to be

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established[77] and skeletal muscle metabolic responses have never been examined. However, in practice, improvements in morbidity and mortality are not yet observed.

## Recommendations for future research

The existing body of research clearly indicates the existence of diurnal rhythms in skeletal muscle and the detrimental metabolic outcomes that can arise from disruption of these rhythms. However, a significant knowledge gap remains regarding how different feeding patterns influence these 24-hour profiles. In particular, it is now important to establish whether these rhythms occur independently from, of or are driven by, feeding pattern (i.e., whether they are driven by endogenous or exogenous clocks, respectively). Furthermore, disruption of circadian clocks as a result of enteral feeding pattern may also lead to insulin resistance, yet no studies to date have examined skeletal muscle clocks in response to divergent feeding patterns. Given the critical role of skeletal muscle in postprandial metabolic regulation[20,35], it is important to establish the temporal responses of this tissue to enteral nutrition delivery pattern.

In addition to furthering mechanistic understanding of divergent feeding patterns, it is important to recognise the need for translational studies to determine whether intermittent feeding with overnight fasting can produce improvements in physiological, hormonal and metabolic responses in critically ill patients. Specifically, we need complementary studies that map tissue-level physiology onto whole-body and clinical outcomes. Given that existing studies of intermittent enteral nutrition still provide nutrition through the night studies aiming to establish the clinical feasibility, tolerability and efficacy of intermittent *diurnal* feeding in critically ill adults would be particularly useful. Additional work should also seek to establish the effects of intermittent enteral nutrition on long-term outcomes (e.g. metabolism, sleep, physical function and cognitive and psychological health).

## Conclusion

Existing research highlights the significance of circadian rhythms in skeletal muscle metabolism and their relevance for critically ill patients. However, the influence of feeding patterns (i.e. temporal variance in nutrient availability) on these rhythms remains unclear. Complementary mechanistic (i.e. in healthy adults) and clinical (i.e. in critically ill patients) studies contrasting the specific metabolic effects of intermittent and continuous nutrition are still required to improve our understanding and provide a more robust evidence base. In turn, this will drive clinical practice in critically ill patients.

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