Can Endogenous or Exogenous Ketosis Tackle the Constraints of Ultra-Endurance Exercise?

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No conflict of interest, financial or otherwise, is declared by the authors.

ABSTRACT

A high-fat, low-carbohydrate, ketogenic diet has already appealed to athletes for a long time due to its purported ability to improve exercise performance and post-exercise recovery. The availability of ketone supplements has further sparked such interest. The review therefore focuses on the potential beneficial impact of exogenous and endogenous ketosis in the context of ultra-endurance exercise.

Summary

Exogenous ketosis may beneficially impact performance and recovery in ultra-endurance athletes.

Key points.

- Performance in ultra-endurance events is affected by multiple constraints including energy deficiency and dehydration, muscle glycogen depletion, lack of sleep, physiological strain and mental fatigue.
- Recent studies observed that ketone supplementation improved post-exercise sleep, attenuated diuresis during exercise, increased muscular angiogenesis and circulating erythropoietin, and attenuated mental fatigue.
- Therefore, we hypothesize that ketone supplementation may beneficially impact performance and recovery in ultra-endurance athletes.
- Conversely, endogenous ketosis has been shown to elicit both beneficial and detrimental effects and therefore we hypothesize that endogenous ketosis is unlikely to improve ultra-endurance performance and recovery.

Keywords: ketone, cycling, ketogenic diet, ketone esters, recovery

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INTRODUCTION

In apparent contrast with the ever-increasing popularity of ultra-endurance events, there is currently a limited understanding of the factors that limit such performances, and how these can be circumvented. Ultra-endurance exercise requires a prolonged physical effort often under extreme environmental conditions (e.g. ≤ 0ºC to ≥ 30ºC) and harsh terrain (e.g. mountain, desert, significant elevation changes, etc.) posing numerous physical and mental challenges (1). Many events also require participants to be fully self-sufficient with a pack weight ranging from 5-19 kg in multi-stage events, while others require the participants to carry a mandatory list of items during the event, further adding to the strain experienced (2). Besides these physical and mental challenges, athletes are also required to adequately manage their energy intake and hydration to achieve optimal performance and to avoid adverse health outcomes. During multi-day stage events, these challenges are further accompanied by sleep deprivation raising potential mental concerns as evidenced by the high prevalence of visual hallucinations and delusions, decreased vigor and lapses of concentration (3). As a result, performance during ultra-endurance events may be limited by multiple factors including mental fatigue, environmental stress, nutritional strategies, energy availability and hydration, cardiovascular strain, and muscular damage and fatigue, while multi-day performance may additionally be influenced by oxidative stress, inflammation, low sleep quality, or a combination of these (4). While other factors may also exist, the review will further focus on those that may be countered by either a ketogenic diet or ketone supplementation.

Many interventions, of which nutritional interventions are the most common, have been suggested to either tackle the constraints during ultra-endurance exercise or to enhance subsequent recovery. These strategies generally focus on refueling, rehydration, and muscle repair. Interestingly, we recently observed that increasing blood ketone bodies – via oral ketone ester ingestion – can beneficially impact multiple constraints of ultra-endurance exercise. Acute effects include improving post-exercise sleep (5), attenuating diuresis during exercise (6–9), increasing circulating erythropoietin(10,11), and attenuating mental fatigue

(12). While long-term adaptations include increasing muscular angiogenesis (10). Therefore, we hypothesize that ketone supplementation may evolve as a novel strategy to beneficially impact performance and recovery in ultra-endurance athletes.

****figure 1 here*****

ENDOGENOUS VS. EXOGENOUS KETOSIS

Ketones bodies, primarily D-β-hydroxybutyrate (βHB) and acetoacetate (AcAc), are fatty-acid derived molecules that are continuously produced by the liver mitochondria and to a lesser extent by astrocytes and kidney cells, from either oxidation of fatty acids or catabolism of ketogenic amino acids (e.g., leucine, lysine, isoleucine, tryptophan, and tyrosine) (13). A low-carbohydrate, high fat "ketogenic diet" (KD) can be used to elevate blood ketone levels. KD requires a carbohydrate intake of <20 $g.day^{-1}$, with some being less restrictive and allowing up to 50 $g.day^{-1}$. Strict adherence to such a KD has been shown to increase βHB levels to 0.8 – 2 mM within 2-4 days (14).

The role of ketone bodies under conditions of energetic and metabolic stress is likely pleiotropic. While ketone bodies act as an additional fuel source, they have also been shown to induce many signaling effects which may impact cellular redox status, gene expression, catabolic processes and sympathetic nervous system activity. The signaling roles of ketone bodies in the context of exercise have recently been described in more detail elsewhere (13).

Next to these endogenous ketotic strategies, ketosis can also be achieved via ingestion of ketone supplements including ketone monoester [(R)-3-hydroxybutyl (R)-3-hydroxybutyrate], ketone salts [(R,S)-βHB salts], ketone diester [(R,S)-1,3-butanediol acetoacetate, bis hexanoyl (R)-1,3-butanediol] or ketone precursors [(R)-1,3-butanediol] (13). While all of these can elevate blood ketone bodies, ketone monoesters (KE) in particular, provide a safe, viable and practical approach to achieve exogenous ketosis (EK) (circulating βHB >0.5 mM for up to 3 hours) in humans without requiring reduced carbohydrate intake (13,15). Ketone salts for instance have a higher incidence of gastrointestinal side effects and elevate blood [βHB] to a lesser extent compared to KE due to their typical racemic nature (for an in-depth overview of the available supplements see Robberechts et al., 2023 (13). Despite the similarity of endogenous *vs.* exogenous ketotic strategies to induce hyperketonemia, they may however provoke divergent effects due to a different interplay with other metabolic substrates. Key differences include elevated lipolysis in KD, while EK acutely lowers plasma free fatty acid concentration. Blood lactate concentrations are similar or higher in KD compared to high carbohydrate diets at the same exercise intensity, but lower in EK (16). Against this background, we aim to provide an up-to-date overview about the impact of endogenous *vs.* exogenous ketosis on ultra-endurance performance, and their ability to impact various constraints of ultra-endurance exercise. The purpose is not to comprehensively discuss all the potential constraints of ultra-endurance performance but to highlight those that may be countered by either KD or EK.

EFFECT OF ENDOGENOUS AND EXOGENOUS KETOSIS ON ULTRA-ENDURANCE PERFORMANCE

Many ultra-endurance athletes are attracted towards the KD and low-carbohydrate diets, because of the reported reduction in gastrointestinal distress compared to high-carbohydrate diets (17), and the ability of the KD to increase fat oxidation rates (18). Indeed, earlier studies showed that adherence to a KD can increase fat oxidation rates during exercise more than twofold (14). However, the increased fat oxidation does not necessarily translate into improved endurance performance, as discussed in a recent review by Louise Burke (14). To date studies have been conducted during endurance exercise, but not ultra-endurance exercise and have found that KD was able to preserve performance at intensities up to 65% of $\dot{V}O_2max$, with no impact at 70% of $\dot{V}O_2max$ and impaired exercise efficiency above 70% of $\dot{V}O_2max$ compared to habitual or high-carbohydrate diet (14). As such, during higher exercise intensities, a low carbohydrate, KD may rather impair exercise performance. In agreement, a meta-analysis concluded that short and higher intensity endurance performance improved with high carbohydrate diets, compared to KDs (19). The negative impact of a KD on performance was also higher in participants with a higher $\dot{V}O_2max$ (19). However, the longer the duration of ketone adaptation the lesser the difference between the KD and the high carbohydrate conditions (19). Taken together, a KD does not seem to translate into improved performance, but moderate intensity performance seems to be maintained. Given that ultra-endurance events are typically performed at lower intensities, it seems plausible to suggest that a KD may result in a similar performance compared to a high-carbohydrate diet, but this has not been investigated so far.

Similar to a KD, exercise performance upon EK is also likely dependent on the exercise context (20). Ketone supplements do not affect repeated sprint performance (21,22) or sprint performance after either a 30 min time-trial (23) or a ~3h simulated cycling race (6,9). Performance in an incremental cycling ramp test and performances of 20 min to 60 min have shown to be either unaffected (20,24,25) or impaired (23,26–28) upon ketone supplementation. Studies involving longer durations reported neutral effects (6,9), while a single study observed a beneficial effect of ketone ester ingestion on a 30 min time-trial following 60 min cycling at 75% of peak power output (29). So far, only one study was conducted during ultra-endurance exercise (*i.e.* 60 to 100km ultramarathon), but no significant difference was observed for running distance, elapsed time, and race pace between the ketone and control groups (12). It should be highlighted that no clear conclusions can be drawn from this study regarding performance given the use of a parallel group design. Nevertheless, apart from performance, this study observed that KE (i) negated the drop in mental alertness during ultra-endurance exercise, (ii) inhibited post-exercise muscular infiltration of macrophages, and (iii) reduced muscular energetic stress as reflected by a lower post-exercise AMPK phosphorylation. This indicates that there are at least various mechanisms by which EK can improve both single and multi-day ultra-endurance performances.

Running economy has been well established to be a good predictor of endurance performance (30). While running economy clearly is a primary determinant in road races, trail running performance in 55, 101, 145 and 175 km distances did not correlate with running economy, even when assessed at a 12% incline to account for race conditions (31). While a KD has been shown to reduce impair exercise economy, the effect of ketone ingestion is more nuanced with studies reporting both negative (9,32), neutral (28), and positive (33,34) effects. Interestingly, the increase improvement in exercise economy during running (33) disappeared when the KE was ingested together with carbohydrates (33). This suggests that the beneficial effect of KE on exercise economy relies on low carbohydrate availability. More work is needed to identify the true effect of KE on exercise economy, but this may provide This provides an alternative mechanism by which KE may either improve or impair ultra-endurance exercise performance. However, it is unclear if changes in exercise economy will translate into altered off-road ultra-endurance performance due to the typical nature of these events (31).

Given the currently unknown effect of endogenous and exogenous ketosis on ultra-endurance performance, the next paragraphs aim to discuss how endogenous and exogenous ketosis may impact constraints experienced during ultra-endurance performance.

CONSTRAINTS OF ULTRA-ENDURANCE PERFORMANCE

Energy availability and fuel oxidation

Matching energy intake with the extremely high accumulated energy expenditure during ultra-endurance exercise is extremely challenging. Compared to road races, this is even more challenging during off-road events (35). To illustrate the importance of appropriate energy intake, a previous study observed that the amount of energy intake per hour negatively correlated with the time to complete an event (36). Energy requirements of ultra-endurance events are determined by the duration and terrain, with previous studies reporting energy expenditures up to 18,000 $kcal.day^{-1}$ (37). Ultra-endurance performance has also been reported to suppress appetite, which may negatively impact recovery needed to maintain performance during multi-day ultra-endurance events (38).

Effect of endogenous ketosis

It has repeatedly been observed that a low carbohydrate ketogenic diet provokes a more than twofold increase in fat oxidation rates during exercise, which has been combined with an increased FAT_{max} (the exercise intensity which elicits maximal fat oxidation rates) (14). This is accompanied by a decrease in carbohydrate oxidation resulting in reduced glycogen breakdown during exercise (39). However, pre-exercise muscle glycogen levels are also reduced upon adherence to a KD, resulting in similar muscle glycogen levels after exercise (39). Furthermore, the increase *vs.* decrease in fat *vs.* carbohydrate oxidation also lowers exercise economy at intensities > 70% $\dot{V}O_2max$ (14). The decreased exercise economy may explain the reduced performance in elite race walkers, but many ultra-endurance events typically occur in mountainous terrain. As mentioned above the decrease in exercise economy may not lead to performance decrements in off-road events.

In addition, long-term (8+ months) habituation to a KD has been shown to not alter the rate of gluconeogenesis either at rest or during exercise compared to long-term adherence to a mixed diet. However, rates of total glucose production and hepatic glycogenolysis were much lower in the KD group (39). This indicates that the rate of gluconeogenesis is not influenced by carbohydrate availability, while the difference in endogenous glucose production is a result of higher hepatic glycogenolysis in the mixed diet group. There was no difference in metabolic rate between the two groups, however carbohydrate oxidation rate was significantly lower and fat oxidation rate significantly higher in the KD habituated group compared to the mixed diet group. In another study, a long-term (6+ months) habituation to KD was associated with higher glucagon levels in ultra-endurance athletes, before, during and after endurance exercise (40). The KD habituated athletes had a maximum fat oxidation rate more than two-fold higher than the athletes following a high-carbohydrate diet (40). This adaptation may be beneficial during ultra-endurance events, especially off-road events when fueling opportunities are limited or challenging. However, during multi-day ultra-endurance performance KD may hinder the recovery process post-exercise as it reduces subjective ratings of appetite even when in a calorie deficit (41). To date it is not clear if KD will be beneficial or detrimental to ultra-endurance performance. Current knowledge suggests that performance may be maintained following long-term adaptation to KD.

Effect of exogenous ketosis

In the first study where the KE was supplemented during exercise, it was observed that KE ingestion altered fuel preference during exercise performed following an overnight fast as evidenced by a reduction in muscle glycogen breakdown and increased utilization of intramuscular triglycerides (29). Furthermore, it was speculated that βHB contributed for 18% and 16% respectively, of total oxygen consumption during endurance performance at 40% and 75% of peak power output (29). The findings suggest that ketone bodies act as an alternative fuel source, sparing muscle glycogen stores for periods of higher intensity (e.g. running up a hill) or towards the end of the event. Nevertheless, Later on, it was shown by the same research group that βHB oxidation only contributed for ~5% to total energy expenditure (34). Even though a 5% contribution may seem minor, it can be of value for ultra-endurance performance, where energy demands are high and protein synthesis is already upregulated (42). Furthermore, *in-vitro* data indicated that ketone body oxidation in muscles is negatively impacted by carbohydrate availability (43). But interestingly, *in-vitro* data also showed that this suppressive effect may be attenuated by long-term (*e.g.,* 24h) ketone body exposure (44). Furthermore, studies have also observed that EK attenuates postprandial glycemia in Type II diabetes (45) and young healthy individuals (46), without affecting endogenous glucose production (45).

In a more recent study, we did not observe a muscle glycogen sparing effect whenever subjects performed a ~3h30min simulated cycling race while consistently receiving 60 g carbohydrates per hour (6). Interestingly, higher blood [βHB] was even related to higher muscle glycogen breakdown during exercise. The exact mechanism behind the observation is not yet known.

Although it does not seem that KE supplementation has a muscle glycogen sparing effect during exercise, it may be an effective strategy to enhance muscle glycogen resynthesis post-exercise. Following a glycogen depletion effort and in the presence of constant high glucose concentration (hyperglycemic clamp at 10 mM) a KE drink increased glucose uptake by 32% and doubled the insulin release compared to a placebo drink, resulting in ~60% higher glycogen resynthesis during the first 2h post-exercise window (47). This was accompanied by increased phosphorylation of Akt^{Thr308}, which plays a central role in insulin-stimulated glucose uptake. This suggests that the increase in muscle glycogen resynthesis occurs via the insulinotropic effect of ketone bodies. In contrast, our research group did not observe changes in muscle glycogen resynthesis following post-exercise KE intake together with carbohydrate (1 $g.kg^{-1}.h^{-1}$) and protein (0.3 $g.kg^{-1}.h^{-1}$) ingestion (48). This contrasting observation is most likely related to differences in glucose and insulin concentrations between the various studies (13), with the insulinotropic effect of ketones only occurring when blood glucose levels are above 8 mM (13). Therefore, it is unlikely that EK may improve glycogen resynthesis during multi-day ultra-endurance events.

Related to energy intake, KE ingestion has been shown to reduce appetite both at rest as well as following exercise (6,49). This effect seems to be mediated via a suppression of ghrelin and may thus potentially impair energy intake during multi-day races. However, in a recent study by our research group, consistent post-exercise and pre-sleep KE ingestion rather caused the opposite effect during a 3-week training overload period (15). Indeed, participants in the KE, but not in the placebo condition, spontaneously increased their energy intake to accommodate for the increase in energy expenditure resulting from the gradual increase in training load. Neither leptin nor ghrelin were different between both groups, but KE attenuated the gradual increase in the stress-sensitive hormone growth differentiation factor 15 (GDF-15) during the overload training period (15). This suggests that long-term KE intake may attenuate the suppressive effect of ultra-endurance exercise on appetite during multi-day events. We also observed that KE ingestion was able to inhibit the decline in BMR in lean female volunteers that were subjected to 4 weeks of 30% caloric restriction without impacting body weight loss (50). Based on these data, long-term ketone supplementation may counteract the development of low energy availability by increasing energy intake, while maintaining BMR during multi-day ultra-endurance exercise.

Physiological constraints and sleep

Ultra-endurance events present participants with a major physiological challenge due to different terrain requirements involving both concentric and eccentric muscle contractions and intense sympathetic modulation (51). It is well-documented that ultra-endurance runners experience cardiovascular strain, oxidative stress, inflammation and muscular damage (52). Sleep quality and quantity can also have a major impact on ultra-endurance performance, especially during multi-stage races wherein optimal recovery is key (53).

Effect of endogenous ketosis on post-exercise recovery and physiological strain

Many studies have looked at the potential ergogenic effects of KDs on endurance performance. But human studies focusing on its post-exercise recovery potential are limited. Nevertheless, a recent study in rodents observed that a 3-week normal protein, KD induced higher mTOR signaling compared to the control group (54). This suggests that in the presence of sufficient protein intake, KD may aid in muscle protein synthesis which will be beneficial during multi-day ultra-endurance events. In addition, the post-exercise recovery process may also be impacted by endogenous ketosis via a reduction of the inflammatory response following strenuous endurance exercise. Although a single day on KD leads to acute oxidative stress in rats, chronic adherence (>1 week) has also been shown to exhibit anti-oxidative properties in healthy rats (55). This is most likely mediated by an activation of the Nrf2 pathway by the KD diet (55). If this finding can be replicated in human studies, KD may result in reduced physiological strain during ultra-endurance performance.

Multi-day ultra-endurance exercise performance will also benefit from improvements in sleep quality and quantity. Related to sleep, a KD diet has been shown to improve sleep quality, specifically increased slow wave sleep (SWS) in healthy, good sleepers compared to the control diet (56). While the study points towards improved sleep quality, there is still a lack of studies investigating the effect of KD on sleep following ultra-endurance performance.

Mechanistically, the metabolism of βHB increases the formation of gamma-aminobutyric acid (GABA) which favors sleep by enhancing slow wave sleep and decreases sleep latency and the amount of waking during sleep (57). This suggests that ketone body metabolism may play a role in sleep control. This effect may for instance be attributed to a modulation of GABAergic neurotransmission, as the activation of GABAergic neurons in the preoptic hypothalamus and basal forebrain are known to increase SWS (58). Another potential mediator is brain-derived neurotrophic factor (BDNF) which has also been linked to sleep disorders (59). The notion that ketone bodies may improve sleep via BDNF largely stemmed from a mice study observing that exercise increased both βHB and BDNF (60). But more recent data, could not confirm that a KD raises circulating BDNF concentrations (61).

Some of these studies indicate that a KD has the potential to reduce the physiological strain experienced during ultra-endurance performance and improve recovery which will be beneficial during multi-day events, but more studies are needed on healthy human participants, especially during ultra-endurance performance.

Effect of exogenous ketosis on post-exercise recovery and physiological strain

Ketone bodies have been shown to elicit both anti-catabolic and anabolic effects as well under healthy and under catabolic conditions (20). A net anabolic effect has also been observed recently during post-exercise recovery. In this study, KE administration following strenuous acute resistance exercise stimulated mTORC1 signaling as evidenced by increased phosphorylation of its downstream effectors ribosomal protein S6 kinase 1 (S6K1) and eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1) post-exercise (48). This is in line with an earlier study wherein βHB infusion reduced leucine oxidation and increased MPS by ~10% in healthy individuals (62). Next to an increase in net muscle anabolic signaling, ketone bodies may also improve skeletal muscle regeneration. This is suggested based on data obtained in mice showing that AcAc stimulated muscle cell proliferation via MEK-ERK1/2-cyclin D signaling, as well as accelerated muscle regeneration by stimulating satellite cell activation, proliferation and differentiation following cardiotoxin induced muscle damage (63). Also, in a mouse model of cancer cachexia ketone diester administration attenuated skeletal muscle atrophy and inflammation-induced catabolism (64). Furthermore, ketone body infusion has also been shown effective to lower muscle protein breakdown during acute LPS-induced inflammation in healthy individuals (65). These findings suggest that ketosis may both attenuate the potential catabolic response induced by ultra-endurance events, as well as stimulate post-exercise muscle anabolism.

Despite these promising effects on skeletal muscle under catabolic conditions, KE administration did not impact muscle damage following an ultramarathon, which is in agreement with the absence of an effect of KE on muscle damage, soreness or recovery following eccentric exercise-induced muscle damage (12,66). However, KE administration seemed to improve muscle energy status as reflected by a lower exercise-induced activation of AMPK (12). This KE-mediated lowering of AMPK activation post-exercise has also previously been reported following resistance exercise (48).

Long-term (i.e. 3 weeks) intake of ketone bodies may also improve post-exercise recovery by increasing skeletal muscle capillarization. Skeletal muscle capillaries are amongst others crucial for nutrient delivery to skeletal muscle, and clearance of metabolites. In a recent study, we observed that consistent KE ingestion post-exercise and pre-sleep increased skeletal muscle capillarization by ~40% during a 3-week overload period, while no changes were observed in the placebo group (10). This was accompanied by a KE-induced increase in skeletal muscle vascular endothelial growth factor (VEGF) and endothelial nitric oxide synthase (eNOS), both at the protein and mRNA level (10). Among other factors, capillary remodeling plays a key role in muscle repair by facilitating blood perfusion, nutrient delivery, and exchange, as well as remodeling of the extracellular matrix (67). Next to stimulating muscle angiogenesis via VEGF signaling, ketone bodies have also been shown to increase circulating erythropoietin (EPO) levels post-exercise (10). EPO is generally known for its hematopoietic effects but has also been shown to induce pro-angiogenic effects under pathological conditions, and as such may also underly the pro-angiogenic response upon KE ingestion (68). Besides angiogenesis, EPO has also been shown to beneficially impact a myriad of other processes in skeletal muscle including stimulation of myoblast differentiation and survival (68). The precise mechanism by which KE increases EPO is still unknown but may include histone H3 lysine 9 (H3K9) acetylation in kidney cells (13). Further research is needed, but current findings suggest that the elevated EPO via KE may enhance recovery after strenuous exercise. These long-term adaptations suggest that ultra-endurance athletes will benefit from EK in the strenuous weeks leading up to a major event or while participating in multi-day ultra-endurance events.

The same 3-week overtraining study mentioned above observed that KE ingestion post-exercise and pre-sleep also blunted the development of most physiological symptoms associated with overreaching (15). This included an inhibition of the increase in overnight urinary catecholamine excretion, indicating a suppression of basal intrinsic sympathetic activity. KE also blunted the overtraining-induced bradycardia during rest, submaximal and maximal exercise. The effect of KE on the sympathetic nervous system may be due to its direct effect at the site of G protein-coupled receptors 41 (GPR41), which are abundantly expressed in sympathetic ganglia (69). GPR41 activity in mice was suppressed by βHB, resulting in a lowered sympathetic tone and heart rate (69). KE also lowered the average heart rate of soccer players during intermittent running exercise compared to the placebo (22). In contrast, other studies observed that an acute bolus of KE before exercise rather increased heart rate during submaximal exercise in cyclists (24,27,28).

Given that elevated nocturnal sympathetic and adrenergic activity are considered to be one of the causes of reduced sleep quality in athletes (70), KE administration may potentially also improve sleep during periods of intensified training. In this perspective, we recently observed that acute KE ingestion counteracted the detrimental impact of late evening strenuous exercise on sleep (5). Strenuous exercise reduced REM sleep and increased wakefulness after sleep onset. But both effects were inhibited by post-exercise and pre-sleep KE ingestion, which also resulted in a 3% increase in sleep efficiency. These effects occurred without alterations in plasma catecholamines or nocturnal adrenaline and noradrenaline excretion. However, nocturnal dopamine excretion was elevated in the KE group, which may explain the increased REM sleep following KE given that cerebral dopamine has been shown to initiate the transition from NREM to REM sleep in mice (71). These findings indicate that while acute KE may increase cardiovascular strain, long-term use may lower the cardiovascular strain experienced during ultra-endurance performance and potentially have a positive impact on sleep quality and quantity.

Hydration

Dehydration is highly prevalent in ultra-endurance athletes and causes both negative mental and performance consequences (72). Further exercising in a dehydrated state increases physiological strain noted by elevated heart rate and core temperature, which may negatively impact performance and health (73).

Effect of endogenous ketosis

To our knowledge, no study has investigated the effect of a KD on hydration status during endurance exercise. However, it is well known that the early stage of KD is associated with water loss, due to a decrease in glycogen storage (74).

Effect of exogenous ketosis

Studies have consistently observed that KE ingestion during exercise suppressed urine production by ~20-40%, suggesting a potential anti-diuretic effect (6–9). This may help athletes to retain euhydration during ultra-endurance events, especially during participation in the heat. The exact physiological mechanism underlying the antidiuretic effect is still not clear, but during a cycling race KE supplementation attenuated the exercise-induced rise in blood

N-terminal proatrial natriuretic peptide (NT-pro ANP) (8). However, given the limited effect of ANP on renal hemodynamics during exercise this is likely insufficient to explain the reduced urinary output. Furthermore, an elevated adrenergic tone in the KE *vs.* placebo condition was also observed, which may decrease renal blood flow, lowering glomerular filtration rate and consequent urine output (8). These data suggest that KE may attenuate dehydration during ultra-endurance exercise.

Cognitive function

Maintaining a high level of cognitive function is essential to achieve optimal performance in ultra-endurance events (75). However, during ultra-endurance events, athletes often push themselves beyond their physical and physiological limits, which can lead to psychological exhaustion. Mental fatigue during ultra-endurance performance manifests subjectively as increased tiredness, lack of energy, decreased motivation and alertness, and behaviorally reduces performance on cognitive tasks as well as physical performance amongst others by impacting the pacing strategy (62).

Effect of endogenous ketosis

The effect of a KD on mental fatigue or cognition has not been investigated yet during exercise in humans. However, the KD has been shown effective to improve cognitive function in patients with diseases such as Alzheimer's, Parkinson’s, and epilepsy (76). Such benefits may also be present in response to exercise given earlier data in rats. In this regard, a study observed that in response to a 7-week high fat diet, the extent of ketosis was directly related with better cognitive function and a reduction in the probability of experiencing mental fatigue (77). Furthermore, adherence to a KD for 3 weeks was sufficient to improve dopaminergic activity in the motor and somatosensory cortex regions in mice (78). Nevertheless, it remains to be identified if such KD-induced reduction in mental fatigue also occurs in humans during (ultra-endurance) exercise.

Effect of exogenous ketosis

Recent evidence suggests that KE supplementation may not only reduce the physiological strain experienced during ultra-endurance performance but may also preserve cognitive function. In this respect, Evans and Egan (2018) observed that KE inhibited the decline in executive function following exhaustive exercise in team sport (22). We recently observed a comparable finding in ultra-marathon runners, wherein KE before and during an ultramarathon eliminated the decline in cognitive function (12). This included an inhibition of the ultramarathon-induced decline in reaction and movement times, together with an inhibition of the increased number of false alarms during a rapid visual information processing task (12). Evidence that KE can indeed alleviate an exercise-induced decline in cognitive function is also supported by the fact that KE attenuated the drop in the number of correct answers and the increase in reaction time induced by a 45-minute simulated soccer match and pre-induced mental fatigue (79). Similar to a KD, these beneficial effects on cognitive function seem to be only present whenever cognitive function is impaired, and as such KE are most likely not able to upregulate normal cognitive function.

A decrease in brain dopamine signaling is in part responsible for developing mental fatigue during ultra-endurance performance (80). Following a 60 to 100-km trail run the KE group had a twofold increase in plasma dopamine concentration with no changes in the control group. Total nocturnal excretion of dopamine was elevated by 20% upon KE intake following a single day of strenuous exercise (5). However, dopamine does not cross the blood-brain barrier, and further work is needed to identify if KE can increase dopamine concentrations in the brain during ultra-endurance exercise. Interestingly, elevating plasma βHB concentrations has also been shown to increase cerebral blood flow while reducing vascular resistance (81). Therefore, the rise in plasma dopamine with KE intake, may help explain the maintenance of mental alertness and decision making during ultra-endurance performance.

CONSIDERATIONS FOR FUTURE RESEARCH

Current literature is insufficient to warrant the use of a KD or ketone supplementation to acutely enhance physical performance, but evidence suggests that there may be potential benefits in ultra-endurance performance, particularly during multi-day events. Based on the characteristics of ultra-endurance performance it seems plausible that long-term adaptation to a KD may at least result in similar performance to a traditional high-carbohydrate diet. More research is needed on the recovery potential of KDs and their effect on hydration, sleep and mental fatigue during ultra-endurance performance. Long-duration studies are especially needed to investigate the potential of KD on ultra-endurance once ketone-adapted.

~~Carbohydrates co-ingested with KE seems to blunt the ergogenic potential of KE both in its potential to serve as an additional energy source, as well as in improving running economy. However, prolonged EK may attenuate this combined effect making it highly interesting for ultra-endurance exercise.~~ Future studies should investigate multi-day endurance performance combined with prolonged exposure to EK and investigate how it potentially alters metabolism and performance. Multi-day endurance events will provide an ideal setting to investigate the recovery potential of both a KD and EK. A potential anti-diuretic effect of KE has repeatedly been shown and warrants further investigation, in terms of the mechanism behind this finding and its potential outcome in ultra-endurance performance. The work on the link between the maintenance of both cognitive function and sleep upon KE respectively during and following exercise is promising and future studies should further investigate the recent finding of increased dopamine release. Future studies should also focus on the appropriate dose and timing of KE.

CONCLUSION

Ultra-endurance performance is characterized by high levels of physical and mental strain. A KD may be promising in reducing fatigue, muscle damage and mental fatigue during endurance performance, but to date all these findings are based on studies performed on either patients or rodents. Furthermore, there is robust evidence that a KD improves fat oxidation rates, which may also be beneficial for ultra-endurance performance. Nevertheless, these potential beneficial effects seem to be counteracted by negative effects such as a decrease in mechanical efficiency. As such, we hypothesize that a KD may result in similar, but not improved, performance and recovery in ultra-endurance exercise.

Conversely, ketone ingestion has shown the potential to tackle many constraints of both single and multi-day ultra-endurance exercise. This primarily includes an attenuation of exercise-induced mental fatigue, dehydration and sleep disturbances. Ketone supplementation may also improve ultra-endurance performance by acting as an additional fuel source, by lowering cardiovascular strain during long-term use, and by attenuating metabolic dysregulations. This is accompanied by a potential to improve post-exercise recovery by facilitating restoration of (muscular) energy balance, increasing glycogen resynthesis, and a stimulation of net muscle anabolism. Therefore, we hypothesize that ketone ingestion may enhance performance and recovery during ultra-endurance exercise.

AUTHOR CONTRIBUTIONS

L.E. drafted the manuscript, prepared the figure, and conceived the article. E.T. and K.K. critically evaluated the manuscript. C.P. drafted the manuscript and conceived the article. All authors approved the final version of the manuscript.

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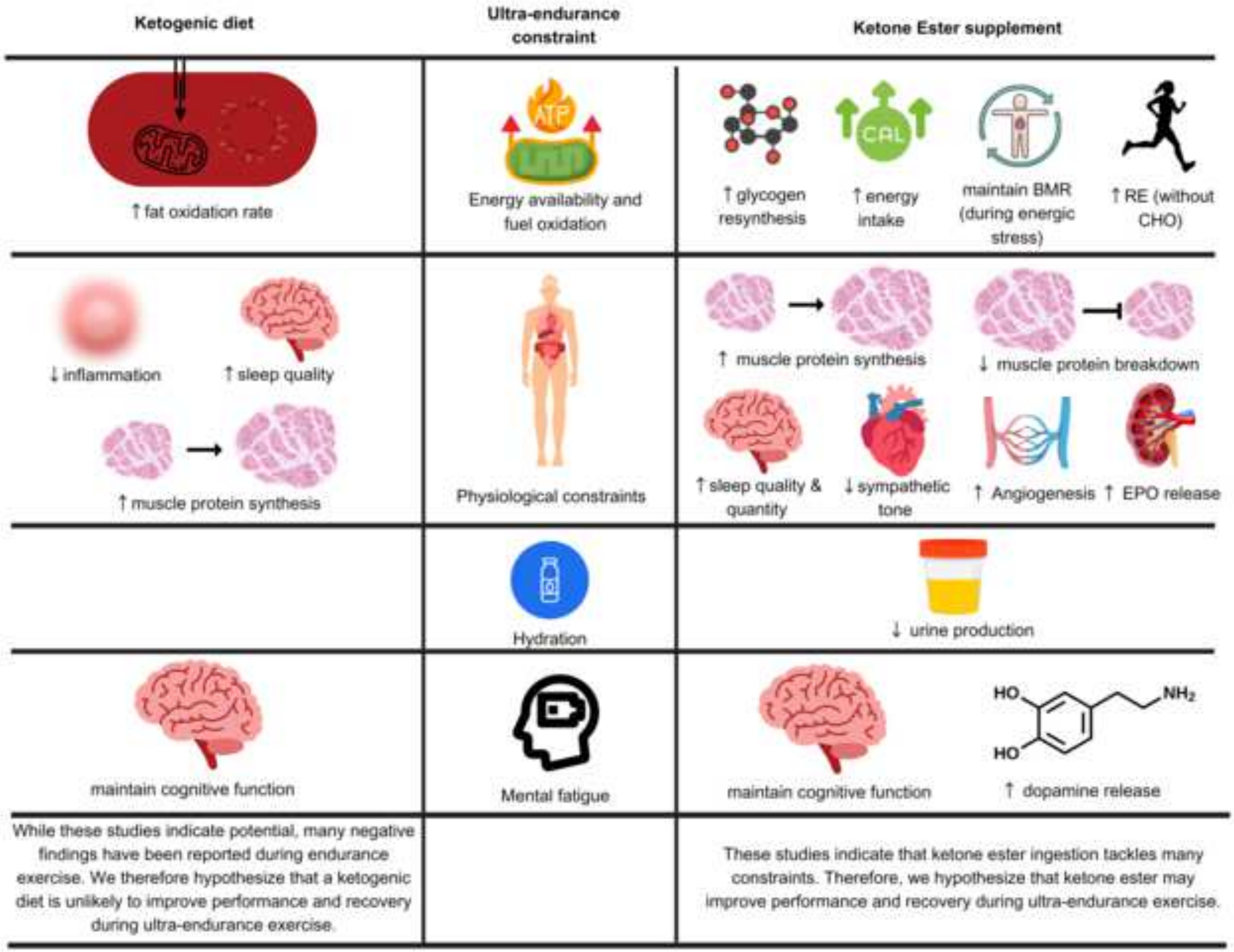
FIGURE LEGEND

Figure 1: An overview of the different physiological effects by which either ketogenic diet or exogenous ketosis (KE in particular) may impact ultra-endurance constraints to potentially improve recovery and performance.

KE: ketone ester; BMR: basal metabolic rate; CHO: carbohydrates; RE: running economy; EPO: erythropoietin.

Figure


Ketogenic diet
Ultra-endurance constraint
Ketone Ester supplement
↑ fat oxidation rate
ATP
Energy availability and fuel oxidation
↑ glycogen resynthesis
CAL
↑ energy intake
maintain BMR (during energic stress)
↑ RE (without CHO)
↓ inflammation
↑ sleep quality
↑ muscle protein synthesis
Physiological constraints
↑ muscle protein synthesis
↓ muscle protein breakdown
↑ sleep quality & quantity
↓ sympathetic tone
↑ Angiogenesis
↑ EPO release
Hydration
↓ urine production
maintain cognitive function
Mental fatigue
maintain cognitive function
HO
HO
NH2
↑ dopamine release
While these studies indicate potential, many negative findings have been reported during endurance exercise. We therefore hypothesize that a ketogenic diet is unlikely to improve performance and recovery during ultra-endurance exercise.
These studies indicate that ketone ester ingestion tackles many constraints. Therefore, we hypothesize that ketone ester may improve performance and recovery during ultra-endurance exercise.