Perspective: Ketone Supplementation in Sports—Does It Work?

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ABSTRACT

Oral ketone supplements have gained popularity in recent years. There is biological rationale for a potential ergogenic effect of this type of supplement, as they might not only alter muscle fuel preference during exercise (and promote glycogen sparing, with potential benefits for endurance performance) but also favor cognition performance during exertion or muscle glycogen synthesis after exercise. However, as discussed in this Perspective, evidence to date does not support a benefit of acute ketone supplementation on sports performance, cognition, or muscle recovery [although further research with long-duration exercise (i.e., >60 min), is needed], and the evidence for chronic supplementation is sparse. In addition, acute intake of ketone supplements might be associated with gastrointestinal symptoms, and further research is warranted on the long-term safety of repeated use of ketone supplements. In summary, there is currently insufficient evidence to support the overall effectiveness of ketone supplements in sports. *Adv Nutr* 2021;12:305–315.

Keywords: endurance, sports nutrition, ergogenic, supplementation, ketogenic

Introduction

Myofiber glycogen is the main energetic substrate for muscle work during intense endurance exercise (e.g., in the last mountain ascent of a Tour de France stage). As such, depletion of muscle glycogen stores accelerates fatigue onset during such strenuous tasks [1] and carbohydrate loading has been traditionally viewed as the best nutritional strategy before and during endurance exercise, in order to preserve muscle glycogen deposits and thus to prevent premature fatigue [2]. However, in recent years, ketone supplementation has been proposed as an alternative (or complementary) strategy that might also boost endurance sports performance, yet through different metabolic pathways [3]. The purported ergogenic effect of ketone supplementation is attracting scientific [1, 4, 5] as well as mass media attention, with these supplements allegedly used by numerous elite endurance athletes, notably professional cyclists.

There is a biological rationale to support a potential ergogenic effect of ketone supplementation (**Figure 1**). Ketone bodies (acetoacetate, acetone), as well as β-hydroxybutyrate (βHB) synthesized from acetoacetate (all 3 herein considered as ketone bodies for the sake of simplicity), are produced from fatty acids by the liver mitochondria during periods of energy deficiency [prolonged fasting, ketogenic (low-carbohydrate) diets, long-duration exercise] to replace glucose as the primary energy substrate for extrahepatic tissues like the brain, heart, or skeletal muscle [1]. Ketone bodies seem to inhibit glycolytic flux [6], and therefore oral acute ketone supplementation before or during exercise (which results in increased concentrations of ketone bodies in plasma) might represent an extra energy supply for muscle work, potentially sparing muscle glycogen stores [1, 4]. In addition, ketone bodies would represent a more efficient energy substrate than glucose or fatty acids because the activation of the former into an oxidizable form (in a reaction catalyzed by succinyl-CoA:3-oxoacid CoA transferase) does not require ATP [7], thereby enabling generation of more muscle work for a given energy cost [5].
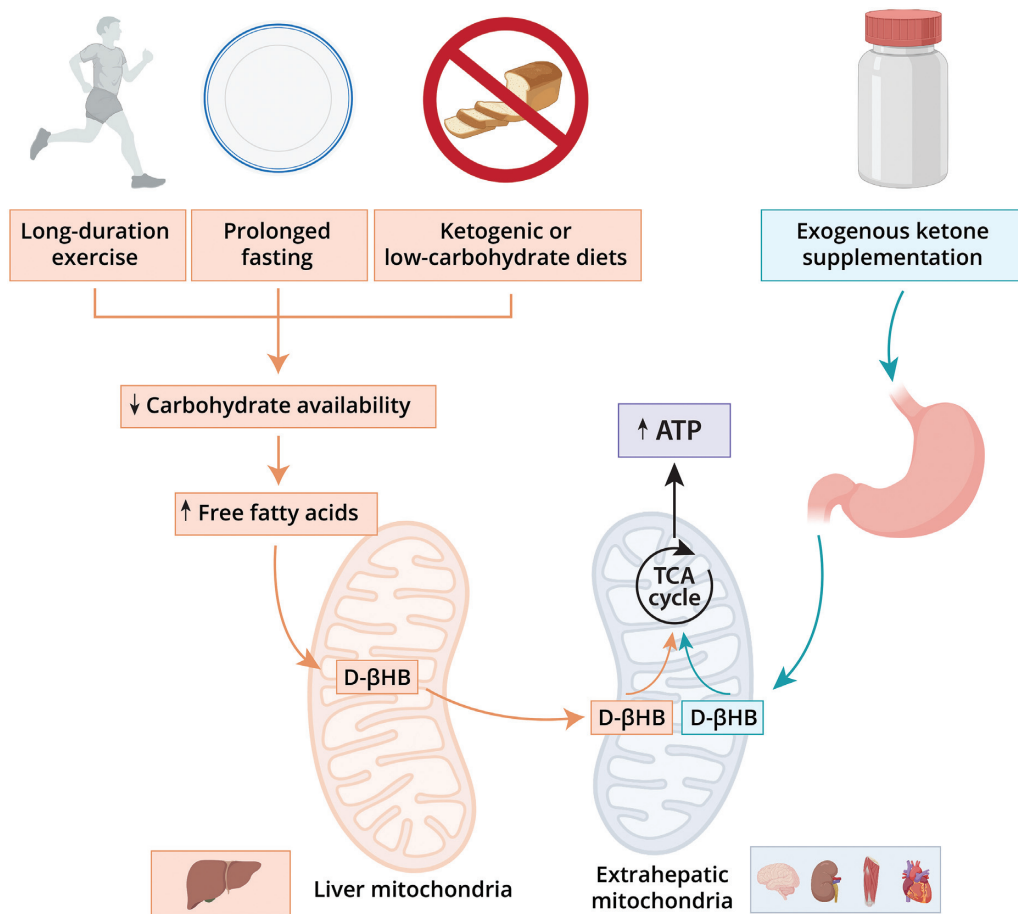
FIGURE 1 Ketosis and ketones: effects on mitochondrial metabolism. D-βHB, D-β-hydroxybutyrate; TCA cycle, tricarboxylic acid cycle.

Despite the purported benefits of ketone body supplements (herein simply "ketone supplements") on sports performance the actual evidence is controversial, and indeed, a recent systematic review concluded that the results provided across studies are mixed and equivocal (8). A recent meta-analysis by our research group concluded that acute (i.e., before or during an exercise bout) ketone supplementation seems to exert no consistent effects on exercise performance (9), although no information was provided regarding the effects on other important outcomes for sports such as cognitive performance or postexercise recovery. Moreover, the effects of chronic (i.e., repeated daily over a period of time) ketone supplementation were not assessed. Under this context, the present Perspective aims to summarize and discuss the evidence that is currently available on the physiological and exercise performance effects of both acute and chronic oral ketone supplementation on exercise performance in humans (as typically assessed in healthy, usually well-trained individuals) (**Table 1**). The potential effects on cognitive performance during or after fatiguing exercise and on postexercise muscle recovery are also discussed, as well as avenues of future research.

Current Status of Knowledge

Sports performance

A seminal study by Cox et al. (3) reported an improvement in simulated endurance bicycling performance with acute administration of ketone esters along with carbohydrates (dextrose) in trained athletes, as reflected by a slight (~2%), albeit significant, increase in the total distance covered during a fixed time (i.e., 30 min) on a cycloergometer compared with the administration of carbohydrates alone. These results must be contextualized in the sports competition setting, with the percentage difference in total performance time between the 1st and the 10th rider in the general classification of the Tour de France usually <1%. The study by Cox et al. indeed contributed to the growing popularity of ketone supplements. However, subsequent studies have failed to replicate performance benefits with acute ketone supplementation (10, 11–13, 14, 15–17, 18) and some authors have in fact reported decrements in performance (19, 20). In addition, a recent meta-analysis by our group—including 13 studies in total—found that acute ketone supplementation has no effect on exercise performance (Hedges' $g = -0.05$; 95% CI: $-0.30, 0.20$; $P = 0.682$) (9).

TABLE 1 Summary of the human studies assessing the effects of ketone supplements on exercise performance, cognition during or after exertion, or postexercise recovery

Study (reference)	Participants	Acute/chronic[1]	Supplementation	Control intervention	Exercise	Main results (ketones vs. control)
Cox et al. (3)[2]	8 endurance athletes	Acute	Ketone ester (573 mg/kg body weight) and dextrose before exercise, under fasting conditions	Taste- and color-matched CHO drink	1-h steady-state workload at 75% of Wmax followed by a 30-min TT	↑ Performance; ↑ plasma D-βHB, ↓ FFA, glucose, and lactate during exercise
Dearlove et al. (10)	12 trained participants	Acute	Ketone ester [330 mg/kg body weight of (R)-3-hydroxybutyrate (R)-1,3-butanediol] before exercise, under fasting conditions	Noncaloric drink (bitter-flavored water)	Incremental cycle test to exhaustion	↔ Performance; ↑ plasma D-βHB after exercise; ↑ workload at OBLA; ↓ plasma glucose and lactate during exercise
Evans et al. (21)	19 trained cyclists	Acute	Ketone salts (380 mg/kg body weight) 60 and 15 min before exercise, under fasting conditions	Water	Incremental cycle exercise up to 80% of VO$_{2peak}$	↑ Plasma D-βHB; ↓ glucose before and during exercise; no changes in indirect markers of performance
Evans and Egan (11)	11 male team sport athletes	Acute	Ketone ester [750 mg/kg body weight of R-βHB (R)1,3-butanediol] and CHO before exercise, under fasting conditions	Taste-matched CHO solution	Loughborough intermittent shuttle test [5 × 15 min of intermittent activity followed by shuttle run to exhaustion (lasting ~4 min)]	↔ Performance; ↑ plasma D-βHB; ↑ plasma glucose and lactate during exercise; ↑ cognition
Evans et al. (12)	8 endurance-trained runners	Acute	Ketone ester (573 mg/kg body weight) and CHO before and during exercise, under fed conditions	Taste-matched CHO solution	1 h of submaximal exercise [~65% of VO$_{2max}$) followed by a 10-km running TT (~40 min)]	↔ Performance; ↑ plasma D-βHB during exercise; ↔ cognition
Faull et al. (13)	12 trained participants	Acute	Ketone ester [330 mg/kg body weight of (R)-3-hydroxybutyl (R)-3-hydroxybutyrate] before exercise, under fasting conditions	Noncaloric drink (bitter-flavored water)	Incremental cycle test to exhaustion	↔ Performance; ↑ plasma D-βHB before exercise
Holdsworth et al. (22)	12 well-trained male athletes	Acute	Ketone ester [0.573 mL/kg body weight of (R)-3-hydroxybutyl (R)-3-hydroxybutyrate] under fasting conditions after a glycogen-depleting exercise protocol	Noncaloric drink with sweeteners and citrus flavoring	Intermittent exercise alternating 2-min intervals at 90% and 50% PPO; workload was decreased progressively by 10% PPO as fatigue appeared, until exhaustion (60% PPO)	↑ Plasma D-βHB after exercise; ↑ glucose uptake and endogenous insulin concentration; ↑ muscle glycogen content
James and Kjerulf Greer (23)	10 non–aerobically trained participants	Acute	11,700 mg of ketone salts taken together with decarbonated, noncaffeinated diet cola before exercise after a fast ≥4 h	Decarbonated, noncaffeinated diet cola	Two 6-min stages of the Bruce protocol	↔ Performance; ↑ plasma D-βHB concentration before and after exercise

(Continued)

TABLE 1 (*Continued*)

Study (reference)	Participants	Acute/chronic[1]	Supplementation	Control intervention	Exercise	Main results (ketones vs. control)
Leckey et al. (19)	11 male internationally competitive cyclists	Acute	Ketone ester (250 mg/kg body weight of 1,3-butanediol acetoacetate diester) 30 min and immediately before exercise, under fed conditions	Viscosity- and color-matched drink with bitter flavor	31-km TT on a cycling ergometer (~50-min duration)	↓ Performance; ↓ plasma FFAs, glucose and lactate; ↑ plasma acetoacetate and D-βHB during exercise
O'Malley et al. (20)	10 healthy, recreationally active males	Acute	Ketone salts (300 mg/kg body weight) with lemon juice and stevia 30 min before exercise, under fasting conditions	Lemon juice and stevia	Steady-state exercise at 30%, 60%, and 90% of VT followed by a 150-kJ cycling TT (~11-min duration)	↓ Performance; ↑ D-βHB and total fat oxidation during exercise; ↓ plasma glucose and total CHO oxidation during exercise
Poffé et al. (24)	18 physically active males	Chronic	Ketone ester [25 g of (R)-3-hydroxybutyl (R)-3-hydroxybutyrate] after each exercise session and 30 min presleep during an intensive 3-wk training program, provided along with a 500-mL high-dose protein–carbohydrate drink following exercise	Isocaloric bitter drink containing 16.4 g pure medium-chain triglycerides, provided along with a 500-mL high-dose protein-CHO drink following exercise	3 wk of exercise training that aimed at inducing functional overreaching (2 sessions/d, 6 d/wk)	↑ Plasma D-βHB 30 min postexercise; ↑ training workload in week 3; ↑ TT performance; ↔ body composition; ↓ markers of overreaching (e.g., plasma GDF15 concentrations, urinary catecholamine excretion, and heart rate decrease)
Poffé et al. (14)	12 highly trained male cyclists	Acute	Ketone ester [65 g of (R)-3-hydroxybutyl (R)-3-hydroxybutyrate] provided in 3 boluses ingested 60 and 20 min before exercise, and at minute 30 during the exercise protocol; supplement was provided under fed conditions and subjects ingested CHO before and during exercise (60 g/h)	Viscosity- and taste-matched supplement (with less caloric content than the ketone supplement); subjects ingested CHO before and during exercise	Simulated cycling race consisting of 3 h of submaximal intermittent cycling followed by a 15-min TT and an all-out sprint	↔ Performance; ↑ plasma and urine D-βHB; ↓ plasma glucose following ketone ingestion; ↓ FFAs during exercise; ↔ plasma lactate; ↓ blood pH and bicarbonate concentration during submaximal exercise; ↔ muscle glycogen and intramyocellular triglyceride content and breakdown
Poffé et al. (25)	9 well-trained male cyclists	Acute	Ketone ester [65 g of (R)-3-hydroxybutyl (R)-3-hydroxybutyrate] provided in 3 boluses	Viscosity- and taste-matched supplement; subjects ingested CHO before and during exercise (60 g/h)	Simulated cycling race consisting of 3 h of submaximal intermittent cycling followed by a 15-min	↑ TT performance (only when provided with bicarbonate); ↔ sprint performance; ↑ plasma and urine D-βHB;

(*Continued*)

TABLE 1 (Continued)

Study (reference)	Participants	Acute/chronic[1]	Supplementation	Control intervention	Exercise	Main results (ketones vs. control)
			ingested 60 and 20 min before exercise, and at minute 30 during the exercise protocol; supplement was provided under fed conditions and subjects ingested CHO before and during exercise (60 g/h); the ketone ester supplement was provided with and without bicarbonate (300 mg/kg)		TT and an all-out sprint	↔ blood glucose and lactate; ↓ blood pH and bicarbonate concentration, but prevented with bicarbonate
Rodger et al. (15)	12 highly trained male cyclists	Acute	Ketone salts (11,700 mg) with sugar-free lemonade 20 min before and during exercise, after a fast ≥2.5 h	Taste-matched placebo diluted in sugar-free lemonade	Submaximal cycling (80% VT2) for 90 min followed by a 4-min TT	↔ Performance; ↑ plasma D-βHB and RER during exercise
Scott et al. (16)	11 male runners	Acute	Ketone ester (500 mg/kg body weight of 1,3-butanediol) and CHO, under fasting conditions 75% was taken before submaximal exercise, and 25% before the TT	Caloric-matched CHO drink	60 min of submaximal running (75% VO_{2max}) followed by a 5-km running TT (~21-min duration)	↔ Performance; ↑ plasma D-βHB; ↓ lactate during exercise
Shaw et al. (17)	9 trained male cyclists	Acute	Ketone ester (350 mg/kg body weight of 1,3-butanediol) with an orange-flavored drink 30 min before exercise and again 60 min during submaximal exercise, after a fast ≥4 h	Orange-flavored drink	85 min of submaximal exercise (85% of VT2) followed by a 7-kJ/kg TT (~29 min)	↔ Performance; ↑ plasma D-βHB after exercise
Vandoorne et al. (26)	8 healthy trained males	Acute	Ketone ester [0.5 g/kg body weight of (R)-3-hydroxybutyl (R)-3-hydroxybutyrate] immediately after a glycogen-depleting exercise protocol and 0.25 g/kg/h thereafter for 5 h; the supplement was provided in the fed state and along with a CHO/protein recovery drink	Isocaloric supplement of long-chain triglycerides that was similar in taste and appearance, provided along with the same recovery drink as in the experimental condition	Unilateral knee extensions at the highest power output possible for 5 min, 9 series of 30 extensions at 30%1RM, and 5 series of 6 extensions at 70%1RM	↑ Plasma D-βHB; ↓ plasma glucose; ↔ plasma insulin; ↑ mTORC1 activation (higher phosphorylation status of S6K1 and 4EBP1); ↓ AMPK activation; ↔ glycogen resynthesis

(Continued)

TABLE 1 (Continued)

Study (reference)	Participants	Acute/chronic[1]	Supplementation	Control intervention	Exercise	Main results (ketones vs. control)
Waldman et al. (18)	15 healthy, recreationally active males	Acute	Ketone salts (11,380 mg of D-βHB) 30 min before exercise, under fed conditions	Caloric-matched drink with similar taste and smell	Four 15-s cycling sprints	↔ Performance; ↑ plasma D-βHB after exercise; ↔ cognition

Note: for simplicity purposes, only the main results related to performance and to significant changes in physiological changes are shown. AMPK, AMP-activated protein kinase; CHO, carbohydrate; D-βHB, D-β-hydroxybutyrate; FFA, free fatty acid; GDF15, growth differentiation factor 15; mTOR1, mammalian target or rapamycin; OBLA, onset of blood lactate accumulation; PPO, peak power output; RER, respiratory exchange ratio; RPE, rating of perceived exertion; S6K1 (ribosomal protein S6 kinase β1, also known as p70S6 kinase); TT, time trial; VO_{2max}, maximal oxygen uptake; VO_{2peak}, peak oxygen uptake; VT, ventilatory threshold; VT2, second ventilatory threshold; Wmax, maximal power output; 1RM, 1 repetition maximum; 4EBP1, eukaryotic translation initiation factor 4E (eIF4E)-binding protein 1; ↑, increase; ↔, no change; ↓, decrease.

[1]"acute" refers to supplementation before or during an acute exercise bout only, whereas "chronic" refers to repeated supplementation over days.

[2]The study by Cox et al. included several experiments, but only the one reporting performance measures is shown in the table.

Numerous factors could potentially influence the effects of ketone supplements on performance—whether these are positive, neutral, or negative—notably the type and dose of the supplement ingested. However, studies using both ketone esters and salts at different dosages (e.g., 330 vs. 750 mg/kg of body weight) have failed to demonstrate beneficial effects on performance. Moreover, some studies have reported no benefits on sports performance despite acute supplementation resulting in similar [∼3 mmol/L; range: 2.6 to 5.2 mmol/L (14)] if not higher [3.7 mmol/L (10)] plasma ketone concentration than that observed by Cox et al. (∼2–3.5 mmol/L) (3).

The effects of acute ketone supplements might also vary depending on the test used for assessing sports performance. In this regard, different endurance exercise modalities have been studied, notably cycloergometer-simulated time trials (lasting 4–50 min) with performance assessed as maximal distance covered in a given time (3) or total time (or average power output) to complete a fixed distance (12, 19, 20, 15–17), incremental cycloergometer (10) or shuttle run tests to exhaustion (11), as well as protocols with a predominant anaerobic component, such as 15-m running sprints (11) or the Wingate anaerobic test (18). Yet, the Cox et al. study was the only one to report performance benefits. The studies that applied the more "ecologically valid" time trials found no beneficial effects after acute oral intake of ketone supplements, such as in the study by Leckey et al. (19), who found a detrimental performance effect (−2%) after acute ingestion of ketone esters in professional cyclists during a 31-km time trial that simulated a road-cycling world championship course. Moreover, we have found no meta-analytical evidence for an effect of acute ketone supplementation on time trial performance (9).

It must be noted, however, that most studies have assessed performance using tests with a duration <60 min. In this effect, although the glucose-sparing effect of ketone supplementation could be potentially beneficial for performance, ketones could also impair carbohydrate metabolism and consequently reduce performance during intense endurance exercise, which relies mostly on muscle glycolytic flux for rapid provision of energy. Indeed, muscle glycogen–derived ATP plays a key role in cellular functions whose failure might accelerate onset of fatigue, notably calcium handling by the sarcoplasmic reticulum (27). In fact, other strategies aiming at reducing reliance on muscle glycogen during exercise (e.g., low-carbohydrate, high-fat diets) have failed to provide clear benefits on competitive performance, and might reduce the capacity to sustain high-intensity exercise (28). Burke et al. (29) reported that a ketogenic diet increased muscle fat oxidation rate in elite race walkers but, on the other hand, impaired exercise economy and performance at race intensities. These results have been replicated in a different cohort of elite race walkers, with ketogenic diet impairing endurance performance in a 10,000-m test even if coupled with carbohydrate loading during the days before testing (30). McArdle's disease (glycogenosis type V) can provide mechanistic insight into the importance of muscle

glycogen for intense endurance exercise performance. This condition is a myopathy caused by an inherited deficiency of the skeletal-muscle isoform of glycogen phosphorylase, "myophosphorylase." Because this enzyme catalyzes the breakdown of glycogen into glucose 1-phosphate in muscle fibers, patients are unable to obtain energy from their muscle glycogen stores (31) and show very poor aerobic capacity (32) and extremely low muscle efficiency during endurance exercise (33).

In turn, it has been reported that muscle fat oxidation rate is higher in "keto-adapted" athletes than in those who consume a high-carbohydrate diet (34), with this adaptation being potentially beneficial for moderate-intensity exercise performance (e.g., ultra-endurance exercise). Indeed, greater fat oxidation rates during a simulated 100-km cycloergometer time trial as well as a higher power output during a subsequent critical power test were reported in endurance athletes who followed a 12-wk ketogenic diet compared with their peers who followed a high-carbohydrate diet (35). A positive association was recently found between the increase in plasma ketone concentrations during a multistage ultramarathon (240 km) and average running speed in the race (36), suggesting that acute ketone supplementation might be beneficial during long-duration low/moderate-intensity endurance exercise. Indeed, in the latter, reliance on muscle glycogenolysis for energy provision is expected to be lower than in shorter, more intense events. In this regard, a recent study in highly trained cyclists by Poffé et al. (14) assessed the effects of acute ketone ester supplementation on performance during both a 15-min time trial and a maximal sprint following 3 h of intermittent cycling, which aimed to replicate actual cycling racing. The authors found no benefits on performance indicators (14). Further research is needed to determine if acute ketone supplementation might exert some benefits on long-duration endurance exercise performance.

It must be noted that some authors supplied less carbohydrate along with the ketone supplement than in the control (non-ketone) supplement in order to match the energy intake of both acute interventions (60 vs. 110 g of carbohydrate for the ketone ester and control supplement, respectively) (16). It can be thus hypothesized that the lower availability of carbohydrates can potentially impair high-intensity performance. However, in the abovementioned study by Scott et al. (16), which did not find significant benefits with acute ketone supplementation, all participants ingested a relatively high carbohydrate intake (≥60 g/h) together with the ketone supplement, which would meet current recommendations for carbohydrate intake for an effort of such duration (<1 h) (37). Moreover, other studies that supplied the same amount of carbohydrates in both the ketone and control intervention also failed to report an ergogenic effect of acute ketone supplementation (11, 12, 19, 14).

It has also been hypothesized that acid-base disturbances after supplementation with ketone esters (as reflected by reductions in blood pH and bicarbonate concentration) might overshadow the ergogenic potential of exogenous ketosis (14). In this regard, a recent study reported that the ingestion of oral sodium bicarbonate along with a ketone ester supplement prevented the drop in blood pH, resulting in an improved time trial performance (by ∼5%) compared with the ingestion of placebo, bicarbonate, or ketone ester alone, respectively (25).

Metabolic effects

Controversy exists as to whether oral ketone supplements can produce a meaningful metabolic effect during exertion. The study by Cox et al. reported that, along with increased plasma concentrations of D-β-hydroxybutyrate (D-βHB; ∼2–3.5 mmol/L) and the abovementioned small but significant performance improvement (∼2%), ketone ester supplementation induced a shift in metabolic fuel preference during exercise, with reduced muscle carbohydrate oxidation and subsequent preservation of muscle glycogen stores as compared with the ingestion of a carbohydrate drink (3). It can, however, be discussed that when participants ingested the ketone ester supplement they consumed less carbohydrate. This, together with the fact that exercise was performed in the fasted state, could have likely contributed to a lower utilization of carbohydrates (2). Mixed evidence also exists for the effects of ketone supplements on plasma concentrations of ketone bodies, with mean plasma D-βHB concentrations reported to range between ∼0.3 (21) and 0.7 (23) mmol/L after ketone salt ingestion and between ∼0.3 (19) and 3.5 (3) mmol/L for ketone esters. Whether the fact that circulating ketone bodies do not consistently show a high increase after supplementation reflects that they are utilized by gut cells and/or rapidly oxidized by other tissues (e.g., brain) remains to be determined. In addition, the reported effects of ketone supplements on blood lactate concentration during exercise are not consistent, with some authors finding lower concentrations (3, 10, 11, 19, 16)—which would reflect a slower rate of muscle glycogen metabolism—but others finding no effects (21, 12, 20, 15, 17, 18). In the same line, some studies (3, 10, 11, 21, 19, 20, 23,) have found lower plasma glucose concentrations with ketone supplementation, but others (12, 15, 17, 18) have reported no differences compared with a control intervention. In addition, 1 study found a lower respiratory exchange ratio (RER) at light exercise intensities (thereby reflecting a lower rate of carbohydrate oxidation compared with fat oxidation) after acute supplementation with ketone salts, but not at high intensities (20), and others have reported no significant effects (3, 12, 16, 17) or even higher RER values (i.e., higher carbohydrate oxidation rate) after acute ketone supplementation (21, 23, 15). A recent study by Poffé et al. (14) found no differences between acute ketone ester supplementation and a placebo drink on muscle glycogen breakdown during 3 h of intermittent exercise or during a subsequent 15-min time trial, which suggests that this strategy had no glycogen-sparing effects.

Cognitive performance

Cognitive performance is of major relevance in some sports, particularly in those where the ability for fast decision

making can influence performance (e.g., team, combat, or racquet sports). Glucose is the preferred energy source for the brain, but strenuous exercise can reduce bloodborne glucose, thereby contributing to the development of "central fatigue" (38). In situations of prolonged starvation, ketones can substitute glucose as the main energy source for the brain, thereby preventing cognitive impairment (39). Ketone bodies can cross the blood–brain barrier, stimulate acetylation of histones at the brain-derived neurotrophic factor (*Bdnf*) gene promoters, and induce the production of hippocampal BDNF, a neurotrophin that is crucial for brain plasticity and regulation of cognitive function (40–42). Under this context, although controversy exists on the actual association between acute BDNF increases and their immediate effects on cognitive performance (43, 44), it has been proposed that ketone supplements might reduce brain reliance on glucose, increase BDNF production, and thus improve cognitive performance (or attenuate cognitive impairment) during and after strenuous exercise.

Evidence on the effects of ketone supplements on cognitive function is, however, scarce and mixed. On one hand, preclinical data (not related to sports) show that nutritional ketosis (i.e., induced by a ketogenic diet) increases cognitive function in rats (45, 46), and indeed moderate nutritional ketosis has been recommended for people with cognitive impairment (e.g., Alzheimer disease) (47). Moreover, adoption of a ketogenic diet has been recently reported to increase brain ketone utilization and to stabilize brain networks in healthy younger adults, with these effects also corroborated after acute supplementation with an exogenous ketone ester (D-βHB) bolus (48). In the same line, some data suggest that ketone supplements might attenuate the transient impairment in cognitive performance that is frequently observed upon termination of strenuous exercise. For instance, Evans and Egan (11) reported that acute supplementation with a ketone ester reduced the number of incorrect responses during a cognitive test performed after an intermittent exercise protocol until exhaustion compared with a placebo supplement (0 vs. 1.8% of wrong responses, respectively). However, Evans et al. (12) also reported no benefits of acute ketone monoester supplementation on reaction time and a multitasking test assessed before and after a 10-km running trial, and Waldman et al. (18) observed no benefits of acute ketone salt supplementation on cognitive performance after high-intensity intermittent exercise. There is therefore insufficient evidence on the effectiveness of ketone supplements to improve cognitive performance in sports.

Recovery postexertion
Ketone supplementation has been proposed to expedite recovery after exercise, which is paramount in multistage events (e.g., Tour de France). Postexercise administration of ketones together with carbohydrates can increase the conversion rate of glucose to glycogen, thereby promoting muscle glycogen replenishment (1, 6). In addition, ketone bodies could potentially attenuate protein oxidation and thus favor muscle repair (1).

Incubation of mouse skeletal muscle with high doses of ketone bodies after 1 h of exercise activated and inhibited protein kinase B (Akt) and AMP-activated protein kinase (AMPK) pathways, respectively, thereby increasing glycogen repletion during the first 2 h following exercise (49). In humans, Holdsworth et al. (22) reported that acute supplementation with a ketone monoester drink along with a glucose clamp after a strenuous interval exercise session increased insulin concentrations, glucose uptake, and muscle glycogen synthesis in humans compared with the ingestion of a control drink and the same glucose clamp (i.e., under conditions of matched glucose availability). Other authors have reported no effects of acute oral ketone ester supplementation after strenuous exercise on muscle glycogen resynthesis in humans, although they found a higher and lower activation of anabolic (e.g., mammalian target of rapamycin complex-1) and catabolic (AMPK) pathways, respectively, in human muscle tissue along with increased levels of protein synthesis assessed in vitro in murine skeletal muscle myoblasts (26). A recent study found that, compared with no supplementation, chronic ketone ester supplementation (i.e., daily ingestion after exercise and before sleeping for 3 wk) prevented the development of overreaching during a strenuous endurance training program in physically active individuals—as reflected by lower nocturnal concentrations of plasma adrenaline and noradrenaline compared with the control group, as well as higher ability to reach high heart rate values during exercise (24). Moreover, supplementation with the ketone ester allowed for a higher training workload to be tolerated during the third week, tended to prevent the depletion of muscle glycogen (albeit statistical significance was not reached), and elicited greater improvements in time trial performance (24). However, some debate has been raised around these findings due to methodological and statistical concerns (no registration of the trial, potential selective reporting, high risk of type I error, or no information on individual responses) (50, 51). Evidence for the effectiveness of ketone supplements for the enhancement of postexercise recovery is, therefore, still scarce and inconclusive.

Safety
Some critics propose that the World Anti-Doping Agency (WADA) should prohibit ketone supplements, with 1 criterion for a substance to be banned by WADA being the possibility that it might represent an actual/potential health risk to the athlete. This question has not been answered in the case of ketone supplements. Different studies have shown a high incidence of gastrointestinal symptoms (e.g., nausea, abdominal cramps, diarrhea) with acute ketone supplementation (11, 12, 21, 19). Indeed, gut disturbances such as those reported by all participants in the study by Leckey et al. (19) (including one with prolonged vomiting and dizziness, and others with mild to severe symptoms such as nausea or reflux) have been proposed as a potential explanation for the absence of performance benefits with ketone supplements. Controversy exists, however, regarding the comparison of
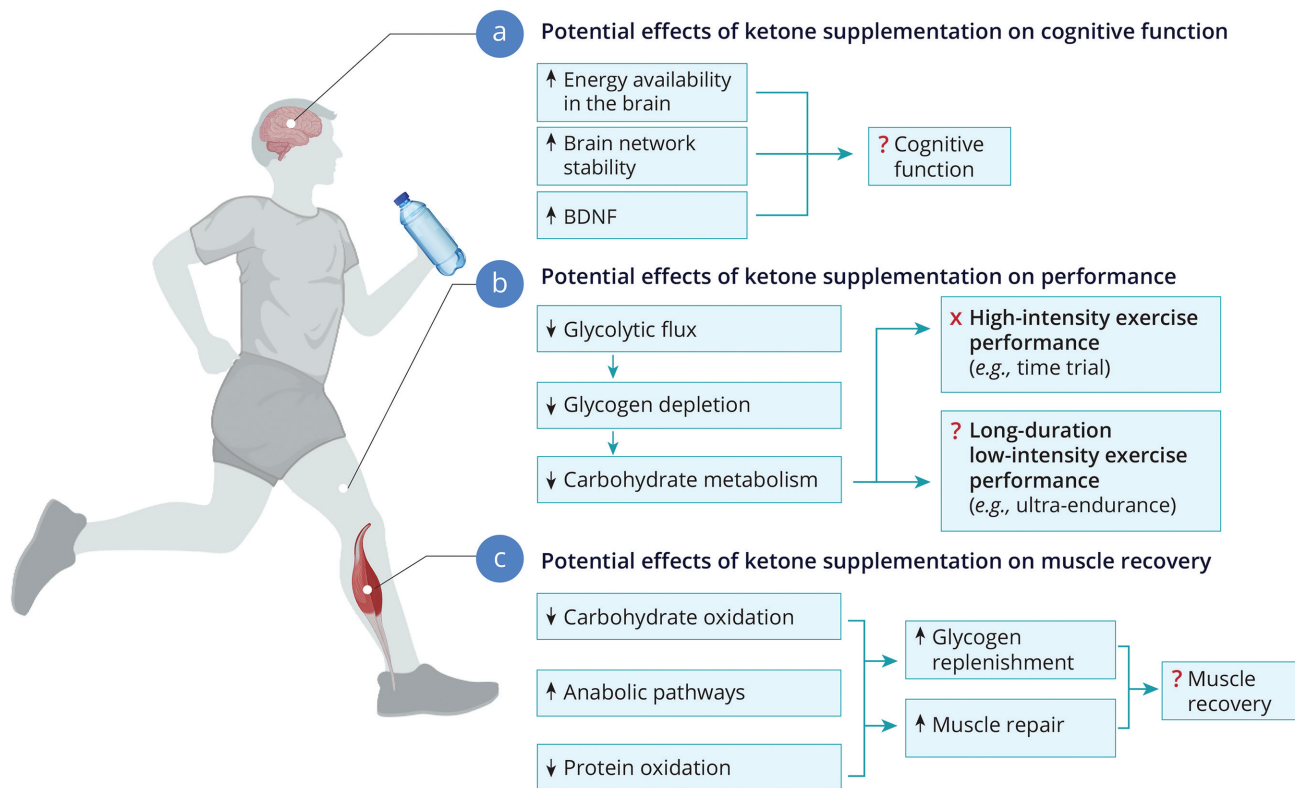
FIGURE 2 Potential mechanisms by which acute ketone supplementation might influence cognitive function, sports performance, or muscle recovery, respectively. BDNF, brain-derived neurotrophic factor.

gastrointestinal symptoms during exercise with oral ketones versus carbohydrate drinks, and some studies have found minimal differences between both types of supplements (19–25, 16). Stubbs et al. (52) recently reported that, at rest, the former result in greater gastrointestinal symptoms, but this difference disappeared if the 2 types of supplements were consumed during exercise. The authors also reported that symptoms seemed to depend on the type and dose of ketone supplement. Indeed, salts would induce greater symptoms than esters (probably due to the coingestion with the former of the inorganic cations sodium and potassium, leading to a hyperosmolar gut lumen and a greater gut water retention) and symptoms seem to increase with higher doses. Further evidence is needed to confirm if acute ketone supplementation–associated gastrointestinal symptoms are comparable to those produced by carbohydrate drinks, as well as to determine if these symptoms might play a role in the lack of performance benefits, and if so, if they could be avoided by modulating the supplementation strategy—for instance, by reducing dosage or using a different type of ketone supplement.

One important caveat in the field is the lack of evidence on the long-term safety of ketone supplements. Physiological elevations in blood ketone concentrations have been potentially linked to a number of multisystemic benefits and, in fact, ketone supplementation has been proposed as a co-adjuvant treatment in several conditions including genetic myopathies or neurodegenerative disease (7). Nevertheless, above-normal concentrations such as those found in patients with uncontrolled diabetes, alcoholic ketoacidosis, or impairments in ketolysis pathways might be associated with higher oxidative stress and inflammation, thereby increasing the production of superoxide radicals and upregulating signaling pathways [e.g., mitogen-activated protein kinase (MAPK)/NF-κB] that induce the expression of adhesion molecules. This can, in turn, lead to the infiltration or transmigration of monocytes with subsequent tissue damage, particularly at the vascular and liver level (53). Moreover, the adaptation to ketosis induced by ketogenic diets is associated, particularly during the first week, with a variety of symptoms known together as "keto flu," including headache, fatigue, nausea, dizziness, gastrointestinal discomfort, and decreased energy. Research should analyze whether repeated ketone supplement administration before exercise sessions could induce some of these symptoms (54).

Conclusions

There is a biological rationale to support a potential ergogenic effect of oral ketone supplementation, especially in its acute form. However, evidence to date shows no clear physiological or performance effects with acute supplementation, and the evidence for a potential benefit on cognition or postexercise recovery is scarce and mixed (**Figure 2**).

Moreover, there is scarce evidence available on the effects of chronic supplementation, and more importantly, evidence is needed regarding the safety of the long-term use of ketone supplements. To date, there is not sufficient evidence to support the effectiveness of ketone supplementation in athletes.

Acknowledgments

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