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The Effect of Acute Ketone Supplementation on Time to Fatigue in NCAA Division I Cross-Country Athletes

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Abstract: This study investigated the effect of a commercially available ketone supplement on heart rate (HR), perceived exertion (RPE), blood lactate, glucose, and ketone concentrations, along with time to fatigue (TTF) during a running task to voluntary fatigue. Twelve NCAA Division I cross-country athletes took part in this randomized, double-blind, placebo-controlled cross-over study. Bayesian methodologies were employed for all statistical analyses, and point estimates were determined to be statistically significant if the 95% highest-density intervals (HDI) excluded zero. TTF was not significantly different between conditions with a $Mean_{diff}$ = 48.7 ± 6.3 s (95% HDI: −335, 424) and a 0.39 probability derived from the posterior distribution, indicating the likelihood that the supplement would increase TTF compared to the placebo control. Lactate concentrations immediately post-exercise were significantly lower in the supplement trial relative to placebo with an estimated $Mean_{diff}$ = −4.6 ± 1.9 mmol; 95% HDI: −8.3, −0.9. There were no significant interaction effects observed for either blood glucose or ketone concentrations nor HR or RPE. These findings imply that the acute ingestion of ketones before running at lactate threshold pace has a low probability of increasing TTF in highly trained Division I runners.

Keywords: ergogenic aid; sports nutrition; running performance

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1. Introduction

Exogenous ketone supplements have emerged as a novel nutritional strategy with purported benefits of enhancing physical performance through altering fuel metabolism. During prolonged aerobic exercise (i.e., running, cycling, or swimming), ketone bodies can make an increasing contribution to performance as an alternative skeletal muscle fuel source. Specifically, the absorption and oxidation of circulating ketones has been shown to increase up to 5-fold during fasted exercise [1–3] with higher rates observed in endurance trained muscle likely due to greater transport capacity and enzymatic machinery [3,4].

Most studies examining the effect of ketone supplementation in athletes have focused on lower body power in trained cyclists [5–10]. The collective findings suggest equivocal, and largely non-significant, results for ketone supplementation increasing power output in the cycling population [6]. However, few studies have considered the impact of ketone supplementation on aerobic performance in trained runners [11–13].

Scott et al. [13] reported that the exogenous supplementation of 1,3-butanediol in addition to carbohydrates ingested prior to a 5 km running time trial did not improve time trial running performance in a population of recreational runners relative to a carbohydrate drink. Similar studies by Evans et al. [11] and Prins et al. [12] revealed that the pre-workout consumption of ketone bodies (ketone monoester and β-hydroxybutyrate-salt + medium chain triglycerides, respectively) had no impact on time trial performance at distances of either 10 km [11] or 5 km [12], respectively. The lack of significant improvements in performance following ketone supplementation is suggestive of no effect, but given the

heterogeneity of study designs, supplements used, and, most importantly, the variability associated with human subjects, we believe further studies are warranted across different subject populations. In the same way that athletes respond, or do not respond, to certain training protocols and/or dietary interventions, there is likely considerable variability in how athletes respond to ketone supplementation. The aforementioned studies did not examine highly trained aerobic athletes, leaving a gap in our knowledge as to how we can better understand factors influencing individual responses to ketone supplementation and how to tailor supplementation strategies in high-performing athletes. Moreover, in competitive sports, marginal performance gains can have a considerable impact. If ketone supplementation were to be effective in enhancing aerobic performance in highly trained athletes, it could have practical implications for elite competitors seeking legal and ethical ways to gain a competitive advantage. We believe this indicates a need for further research examining the potential ergogenic effect of ketone bodies on aerobic performance and undertook an examination of their effects within an active Division I athlete population.

Ketone IQ™ (HVMN Miami, FL, USA) is a new ketone supplement (SUPP) specifically marketed for enhanced endurance performance. Similar to other exogenous ketones, it contains R-1,3-butanediol which, after consumption, undergoes a series of oxidative steps to become beta-hydroxy-butyrate, which is suggested to increase endurance performance [13,14]. At the time of this writing, the effect of Ketone IQ on aerobic performance in Division I cross-county athletes has not yet been quantified. Therefore, the objective of this protocol was to quantify the effect of Ketone IQ on time to fatigue (TTF), heart rate (HR), rating of perceived exertion (RPE), blood lactate, glucose, and ketone concentrations in NCAA Division 1 athletes. We hypothesized that acute supplementation would inhibit the onset of fatigue (i.e., increased TTF) and lead to lower lactate levels compared to the utilization of a placebo (PLC) control.

2. Materials and Methods

2.1. Subjects

Twelve NCAA Division I cross-country athletes (male = 6; age: 20 $\pm$ 0.8 year; height: 176.1 $\pm$ 5.2 cm; weight: 67.7 $\pm$ 7.5 kg, female = 6; age: 20 $\pm$ 1.2 yr; height: 165.9 $\pm$ 3.8 cm; weight: 57.2 $\pm$ 6.2 kg) volunteered for this study. Inclusion criteria required participants to be an active member of the cross-country team. Members of the cross-country team on average work out 5–7 days per week for at least 25 weeks as part of their overall training cycle. Average daily training time is approximately 45–90 min/day at varying intensities. All data collections for participants were conducted within two weeks of their final in-season competition in which they adhered to a low volume training protocol. Subjects were excluded from participation if they had any known cardiovascular, pulmonary, or metabolic disease. Prior to data collection, informed consent was obtained, and each subject completed a health history questionnaire before participation. The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of Creighton University (protocol number: 2004298-01, approval 17 October 2023).

2.2. Study Protocol

All participants concluded their in-season competitions two weeks prior to the initial experimental trial, ensuring consistent training status and peak fitness levels. Throughout the six weeks leading up to the testing, none of the subjects ingested ketone, or other dietary, supplements. Further, the participants were not using any nonprescription medications that could potentially impact the study's results. Each subject participated in both the placebo and supplement conditions as part of this randomized, double-blind, placebo-controlled cross-over study thereby serving as their own controls. The two testing sessions were time matched with a one-week interval between each trial visit. Throughout the study, participants were instructed to adhere to their regular dietary patterns; no dietary intake assessment was collected prior to study participation. Participants were further instructed to avoid both nutritional supplements and nonprescription drugs and refrain from exercise for 24 h before each testing session.

2.3. Supplementation

Fifteen minutes before beginning the running protocol and again 15 min into the warm-up period, the subjects consumed either SUPP (35 mL) or PLC (35 mL) in accordance with the manufacturer's guidelines. The supplement is a commercially available ketone supplement containing R-1,3-butanediol (Ketone-IQ, HVMN, Inc., Miami, FL, USA). The PLC consisted of a non-caloric, sugar-free drink (sugar/calorie/ketone free Ketone-IQ; HVMN, Inc., Miami, FL, USA) similar in taste and appearance to the ketone supplement but containing no active ingredients. A member of the research team, kept unaware of the treatment conditions, prepared the drinks before each testing session. Disclosure of the conditions took place at the completion of all data collection.

2.4. Running Protocol

Fifteen minutes after ingesting their initial beverage, participants underwent a treadmill running task to exhaustion on a Woodway 4Front Treadmill (Woodway, Waukesha, WI, USA). The task included a 20-min warm-up at each individual's "easy" pace (Stage 1), which is followed by a five-minute transition at "marathon" pace (Stage 2), and ultimately running to voluntary fatigue at their "threshold" pace (Stage 3). "Threshold" was calculated as a pace near, or at, their lactate threshold (i.e., 80–90% VO_{2max}). The pacing for each stage was determined using the Jack Daniels' Running Formula (JDRF) [15], incorporating each athlete's personal record achieved during their most recent cross-country season [16].

Of note, we did consider using a time trial method but decided against as we were aiming to maintain an intensity at, or near, lactate threshold during the volitional fatigue task. In this scenario, the athletes should be utilizing aerobic metabolism as the primary energy system with a significant contribution from the oxidative phosphorylation of both carbohydrates and fats. Ketone supplementation in this context may affect substrate utilization and spare glycogen stores while enhancing fat oxidation, thereby delaying the onset of fatigue. Time trials, on the other hand, typically involve maximal or near-maximal effort sustained over the predetermined distance. This intensity often exceeds the lactate threshold, leading to a greater reliance on anaerobic metabolism and anaerobic glycolysis specifically. We chose the volitional fatigue protocol hoping to see a greater impact given the ability to maintain oxidative metabolism relative to the metabolic pathways that we would expect to dominate a time trial event.

2.5. Blood Sampling

Blood sampling for lactate (Lactate Scout portable lactate analyzer; EKF Diagnostics, Cardiff, UK) [17], glucose (Contour NEXT blood glucose monitor; Senseonics, Inc., Parsippany, NJ, USA) [18], and ketones (Ketone BM blood ketone meter; KetoBM LLC, Sheridan, WY, USA) were obtained via finger-stick and immediately processed at the time of measure. Baseline (PRE) levels were assessed following ten minutes of undisturbed seated rest. Additional blood sampling was conducted immediately post-exercise (POST) and ten minutes post-exercise (POST 10).

2.6. Heart Rate and Rating of Perceived Exertion

Heart rate was tracked using an arm-worn heart rate sensor (Polar H10 Heart Rate Sensor, Polar Electro, Bethpage, NY, USA), while the Borg RPE scale (6–20) was utilized for the subjective evaluation of exercise intensity [19]. The Borg Scale was printed and was visually provided to the subject when RPE was required. Heart rate and RPE were documented every three minutes throughout the exercise trials and at the point of voluntary fatigue.

2.7. Statistical Analyses

A power analysis indicated that a sample size of 12 subjects would exceed 80% power for detecting a large effect size (d = 0.89, as per Cohen's classifications [20]) for significant differences at an alpha < 0.05. Bayesian paired samples t-tests were employed to assess variations in TTF between the two conditions (PLC and SUPP). All other measures including

changes in blood lactate, glucose, ketone concentrations, as well as RPE, and HR were examined using Bayesian generalized linear models with Markov Chain Monte Carlo (MCMC) estimation. The D'Agostino–Pearson test was used to confirm data normality, and a non-informative, uniform prior was applied to all analyses. Bayesian model outputs included the posterior mean difference and 95% highest-density intervals (HDIs). Parameter estimates were interpreted as statistically significant when the 95% HDI excluded zero [21]. All statistical analyses were performed in R version 4.2.2.

3. Results

3.1. Time to Fatigue

The time to fatigue was longer in the PLC trial compared to SUPP with an estimated posterior $Mean_{diff}$ = 48.7 ± 6.3 s (95% HDI: −335, 424) and small effect size estimate of 0.13 (95% HDI: −0.72, 0.97). The 95% HDI of the mean difference included zero with only 39.6% of the highest density posterior values being greater than zero. These data denote a low probability (0.39) that the SUPP would generate an increase in TTF (summary results are shown in Table 1).

Table 1. Overview of recorded variables. Data are presented as Mean ± SD. * Indicates a significant difference between the conditions at a respective time point.

	PLC			**SUPP**		
TTF (s)	2154	±	412	2111	±	402
HR (bpm)	189	±	14	189	±	16
RPE	19	±	0.7	20	±	1
Lactate (mmol)						
PRE	4.5	±	1.3	3.5	±	2.3
POST	15.6	±	3.8	13.1	±	4.7 *
POST 10	6.8	±	2.7	9	±	3.5
Glucose (mg/dL)						
PRE	108.9	±	11.8	98.4	±	9.2
POST	135.8	±	37.2	145.7	±	42.1
POST 10	135.6	±	31.1	135.3	±	33.4
Ketones (mmol/L)						
PRE	0.4	±	0.5	0.3	±	0.4
POST	0.3	±	0.3	1	±	0.6
POST 10	0.5	±	0.6	1	±	0.4

3.2. Blood Lactate

Blood lactate concentrations were significantly decreased immediately post-exercise in the SUPP condition relative to the PLC ($Mean_{diff}$ = −4.6 ± 1.9 mmol; 95% HDI: −8.3, −0.9; Figure 1). There were no meaningful differences in lactate concentrations between conditions at either the PRE or POST 10 time point.

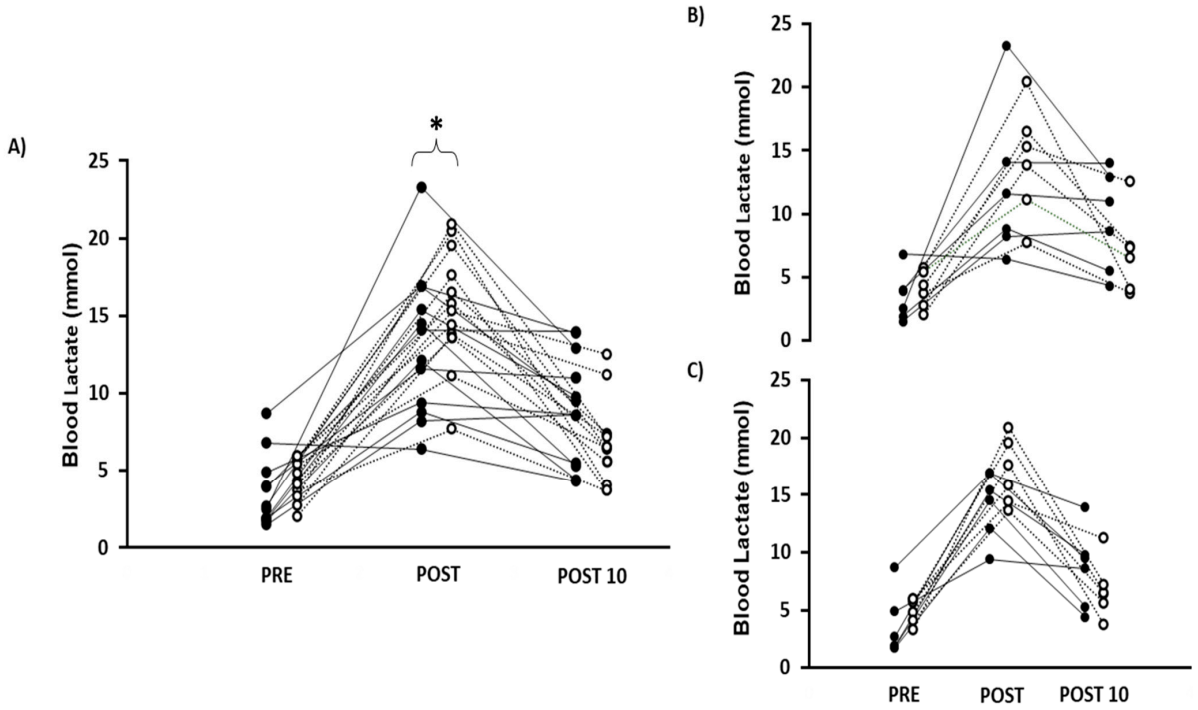

Figure 1. Overall blood lactate concentrations across (**A**) all, (**B**) male, and (**C**) female subjects. ● Indicates SUPP condition. ○ Indicates the PLC condition. * Indicates statistically significant difference between conditions.

3.3. Glucose Concentrations

No significant differences in blood glucose concentrations between conditions at any time point were observed. When examining main effects for time, the PRE measure was significantly lower than the POST measure ($Mean_{diff}$ = −26.3 ± 12.6 mg/dl; 95% HDI: −49.8, −1.0; Figure 2).

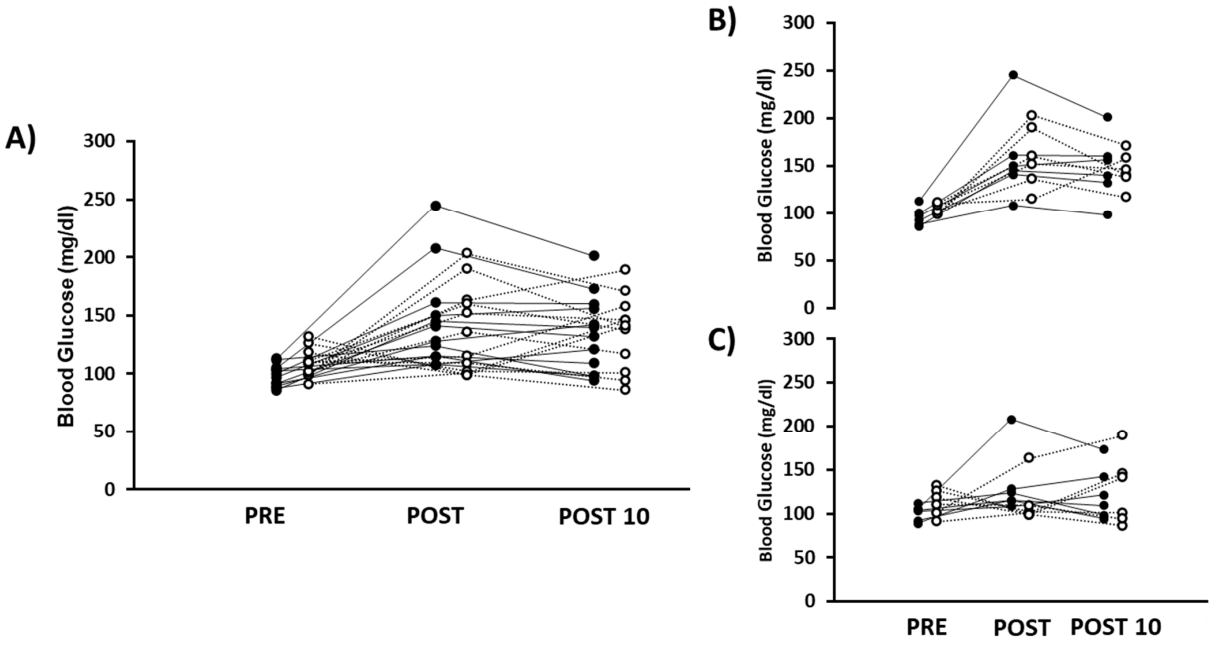

Figure 2. Overall blood glucose concentrations across (**A**) all, (**B**) male, and (**C**) female subjects. ● Indicates SUPP condition. ○ Indicates the PLC condition.

3.4. Ketone Concentrations

No significant differences in blood ketone concentrations between conditions at any time point were observed. When examining main effects for condition, the SUPP condition exhibited significantly higher ketone concentrations relative to the PLC condition ($Mean_{diff}$ = 0.5 ± 0.2 mmol/L; 95% HDI: 0.1, 0.9; Figure 3).

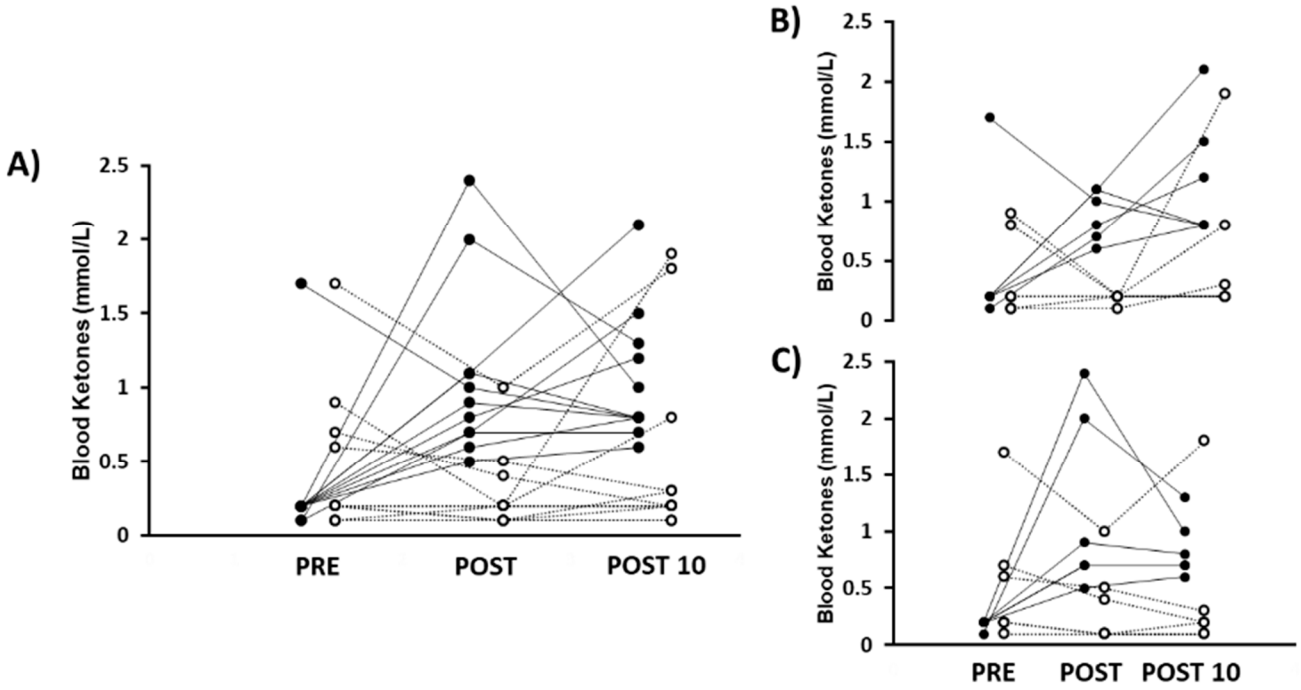

Figure 3. Overall blood ketone concentrations across (**A**) all, (**B**) male, and (**C**) female subjects. • Indicates SUPP condition. ○ Indicates the PLC condition.

3.5. Heart Rate and Rating of Perceived Exertion

Heart rate did not significantly differ between conditions ($Mean_{diff}$ = 0.3 ± 0.5 bpm; 95% HDI: −9.5, 10.3). Similarly, there were no significant differences in RPE across the conditions ($Mean_{diff}$ = −0.5 ± 0.3; 95% HDI: −1.4, 0.3).

4. Discussion

The intent of this protocol was to quantify the acute effect of a ketone supplement on a TTF task in Division I cross-country athletes. The participants, on average, reached voluntary exhaustion 1.2 ± 11.8% faster in the SUPP condition relative to the PLC. These results suggest that the SUPP does not increase TTF in NCAA Division I cross-country athletes. When reviewing individual outcomes, only 7 of 12 subjects exhibited improved performance during the SUPP trial (range: −28.2–11.4%) (Figure 4). Therefore, there is a low probability (~0.39) that this supplement delays the onset of fatigue in the respective population.

Attempts at follow-up analyses to determine whether weight relative to the ketone dosage influenced individual performance during the time-to-fatigue task found no significant correlations nor patterns that would suggest a mechanism of action. There are a number of individual differences including genetic makeup, hydration and dietary status that could have impacted ketone utilization as an energy substrate. We did not, however, conduct a dietary intake analysis as part of this data collection, so we are unable to make an assessment as to whether food intake prior to testing altered the supplements' impact on performance. Beyond this, psychological factors relative to motivation and perceived effort of exertion could have also impacted performance in the time-to-fatigue task. Individual tolerance to taste along with the gastrointestinal effects of this supplement

may have also played a part in the variation we observed in this study. The variability in responses observed is likely due to some combination of physiological and psychosocial factors that will need to be teased out in future work to determine specific mechanisms for supplement-induced changes in performance.

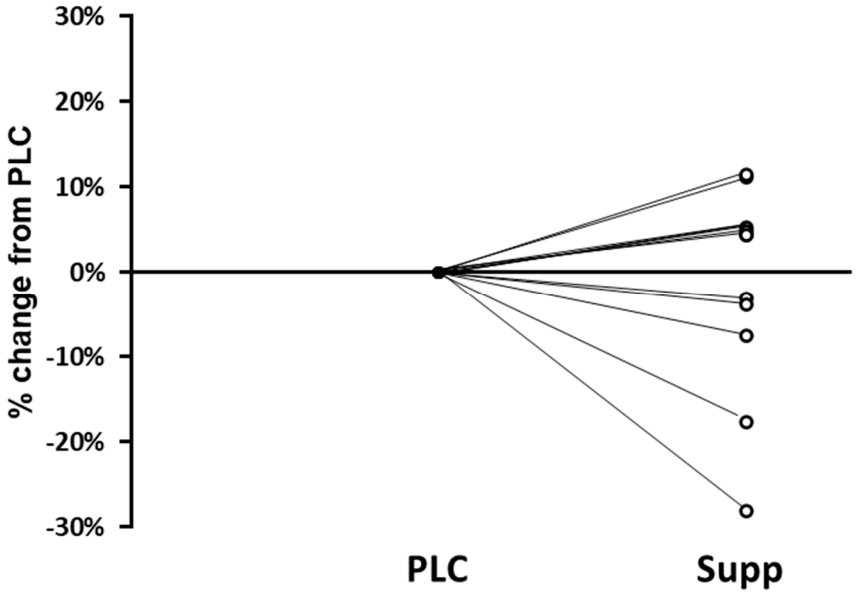

Figure 4. Percentage difference in TTF in the supplement condition compared to the placebo control. The percentage change across conditions was computed using the formula: [((Supplement/Placebo) − 1) × 100]. Among the twelve subjects, seven (58.3%) exhibited an increased TTF in the supplement condition compared to the placebo with an average change of −1.2 ± 11.8%. • Indicates the PLC condition set at the control (i.e. 0) ○ Indicates the change from the PLC condition.

The lack of significant differences between conditions for blood ketone concentration agrees with other studies that showed ketone supplementation prior to exercise induced relatively small increases in blood ketone concentrations [13,22]. While ketone supplements have garnered interest for their potential to enhance physical performance by altering fuel metabolism, ketone esters that are not capable of generating levels of ketosis greater than 2 mmol/L have generally failed to improve performance in endurance athletes [13,23]. Results from a relatively recent systematic review [6] found equivocal evidence across the current literature with only the protocols achieving beta-hydroxy-butyrate concentrations greater than a 2 mmol/L threshold showing a beneficial effect [8,23]. Although circulating ketones tended to increase with supplementation as seen in the SUPP condition of this study, alterations in fuel use were not consistently found [6]. Methodological differences regarding dose, fed state, ketone supplement type, exercise protocol specifics, gastrointestinal tolerance issues, and small sample sizes are all factors likely contributing to the equivocal nature of the research results to this point [6].

The lower lactate concentrations observed post-exercise in the SUPP trial potentially suggests that ketone supplementation either reduces lactate formation or increases clearance rates while running at lactate threshold pace. While not statistically significant, we did observe an increase in blood glucose concentrations immediately post-exercise, which further suggests a glycogen-sparing role of ketone supplementation [23]. These are likely transient effects, however, since a significant difference was only observed at the POST time point. Future research should focus on identifying mechanisms of action with a focus on supplement achieving a higher level of ketosis ($\geq$2 mmol/L).

Studies investigating the impact of ketone supplementation on aerobic performance in Division I athletes are relatively sparse in the existing literature, which may be indicative of a lack of research in the area or, perhaps, a publication bias where it is less likely that

non-significant results are published. The objective, therefore, to quantify the supplement-induced changes on time to fatigue at lactate threshold pace among current Division I athletes is novel given the population but comes with limitations due to both academic and athletic constraints on the study design. Specifically, the research was conducted without imposing dietary restrictions on the subjects before data collection. This approach enabled a precise evaluation of supplement-induced performance differences within the limits of the athletes' real-world training and life cycles. We are lucky in this protocol, as all subjects were at the same stage of training, having followed a standard protocol for approximately 16 weeks before the experiments commenced. The relatively uniform, and highly specific, training status establishes a robust foundation for interpreting these results in the framework of a NCAA Division I cross-country athlete population.

Additionally, we believe this protocol is insightful as Bayesian analyses were incorporated to better capture the deviations intrinsic to human subjects' experiments, particularly those associated with studies involving small sample sizes [21,24]. The analyses reported here present a probability distribution around each estimate; meaning, we can designate not only a probability to our best estimate of the average difference between trials but also acknowledge the range of probable values the parameter could cover [21,24,25]. This probabilistic framework adds a layer of depth to our interpretation, allowing for a more nuanced understanding of the potential variability in the observed effects. By assigning probabilities to expected outcomes, we aim to facilitate better practical application, especially in the context of aerobic performance. This approach allows for a more comprehensive consideration of the uncertainty associated with our findings, contributing to a more informed and robust decision-making process in the context of sport performance.

5. Conclusions

The results of this experimental protocol are in agreement with others and indicate that ketone supplementation prior to a fatiguing task of exercise had no ergogenic effect in trained runners compared to PLC. We also demonstrate here how Bayesian methodologies can better inform practitioners by providing probability assessments to outcomes versus relying on non-informative p-values. We believe additional research in highly trained endurance athletes is needed to clarify if, and under what sport-specific situations, ketone supplements may provide an appreciable benefit.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to the small nature of the dataset and the potential that the privacy of the research participants could be compromised.

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Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Hagenfeldt, L.; Wahren, J. Human forearm muscle metabolism during exercise III Uptake, release and oxidation of beta-hydroxybutyrate and observations on the beta-hydroxybutyrate/acetoacetate ratio. *Scand. J. Clin. Lab. Investig.* **1968**, *21*, 314–320. [CrossRef] [PubMed]
2. Wahren, J.; Sato, Y.; Ostman, J.; Hagenfeldt, L.; Felig, P. Turnover and splanchnic metabolism of free fatty acids and ketones in insulin-dependent diabetics at rest and in response to exercise. *J. Clin. Investig.* **1984**, *73*, 1367–1376. [CrossRef] [PubMed]
3. Evans, M.; Cogan, K.E.; Egan, B. Metabolism of ketone bodies during exercise and training: Physiological basis for exogenous supplementation. *J. Physiol.* **2017**, *595*, 2857–2871. [CrossRef] [PubMed]
4. Rennie, M.J.; Johnson, R.H. Alteration of metabolic and hormonal responses to exercise by physical training. *Eur. J. Appl. Physiol. Occup. Physiol.* **1974**, *33*, 215–226. [CrossRef] [PubMed]
5. Leckey, J.J.; Ross, M.L.; Quod, M.; Hawley, J.A.; Burke, L.M. Ketone Diester Ingestion Impairs Time-Trial Performance in Professional Cyclists. *Front. Physiol.* **2017**, *8*, 806. [CrossRef] [PubMed]
6. Margolis, L.M.; O'Fallon, K.S. Utility of Ketone Supplementation to Enhance Physical Performance: A Systematic Review. *Adv. Nutr.* **2020**, *11*, 412–419. [CrossRef] [PubMed]
7. O'Malley, T.; Myette-Cote, E.; Durrer, C.; Little, J.P. Nutritional ketone salts increase fat oxidation but impair high-intensity exercise performance in healthy adult males. *Appl. Physiol. Nutr. Metab.* **2017**, *42*, 1031–1035. [CrossRef] [PubMed]
8. Poffe, C.; Ramaekers, M.; Van Thienen, R.; Hespel, P. Ketone ester supplementation blunts overreaching symptoms during endurance training overload. *J. Physiol.* **2019**, *597*, 3009–3027. [CrossRef] [PubMed]
9. Shaw, D.M.; Merien, F.; Braakhuis, A.; Plews, D.; Laursen, P.; Dulson, D.K. The Effect of 1,3-Butanediol on Cycling Time-Trial Performance. *Int. J. Sport Nutr. Exerc. Metab.* **2019**, *29*, 466–473. [CrossRef]
10. Waldman, H.S.; Basham, S.A.; Price, F.G.; Smith, J.W.; Chander, H.; Knight, A.C.; Krings, B.M.; McAllister, M.J. Exogenous ketone salts do not improve cognitive responses after a high-intensity exercise protocol in healthy college-aged males. *Appl. Physiol. Nutr. Metab.* **2018**, *43*, 711–717. [CrossRef]
11. Evans, M.; McSwiney, F.T.; Brady, A.J.; Egan, B. No Benefit of Ingestion of a Ketone Monoester Supplement on 10-km Running Performance. *Med. Sci. Sports Exerc.* **2019**, *51*, 2506–2515. [CrossRef] [PubMed]
12. Prins, P.J.; Koutnik, A.P.; D'Agostino, D.P.; Rogers, C.Q.; Seibert, J.F.; Breckenridge, J.A.; Jackson, D.S.; Ryan, E.J.; Buxton, J.D.; Ault, D.L. Effects of an Exogenous Ketone Supplement on Five-Kilometer Running Performance. *J. Hum. Kinet.* **2020**, *72*, 115–127. [CrossRef] [PubMed]
13. Scott, B.E.; Laursen, P.B.; James, L.J.; Boxer, B.; Chandler, Z.; Lam, E.; Gascoyne, T.; Messenger, J.; Mears, S.A. The effect of 1,3-butanediol and carbohydrate supplementation on running performance. *J. Sci. Med. Sport* **2019**, *22*, 702–706. [CrossRef] [PubMed]
14. Pinckaers, P.J.; Churchward-Venne, T.A.; Bailey, D.; van Loon, L.J. Ketone Bodies and Exercise Performance: The Next Magic Bullet or Merely Hype? *Sports Med.* **2017**, *47*, 383–391. [CrossRef] [PubMed]
15. Daniels, J. *Daniels' Running Formula*, 3rd ed.; Human Kinetics: Champaign, IL, USA, 2014.
16. Scudamore, E.M.; Barry, V.W.; Coons, J.M. An Evaluation of Time-Trial-Based Predictions of VO_{2max} and Recommended Training Paces for Collegiate and Recreational Runners. *J. Strength Cond. Res.* **2018**, *32*, 1137–1143. [CrossRef] [PubMed]
17. Hart, S.; Drevets, K.; Alford, M.; Salacinski, A.; Hunt, B.E. A method-comparison study regarding the validity and reliability of the Lactate Plus analyzer. *BMJ Open* **2013**, *3*, e001899. [CrossRef] [PubMed]
18. Harrison, B.; Brown, D. Accuracy of a blood glucose monitoring system that recognizes insufficient sample blood volume and allows application of more blood to the same test strip. *Expert. Rev. Med. Devices* **2020**, *17*, 75–82. [CrossRef] [PubMed]
19. Borg, G.A. Psychophysical bases of perceived exertion. *Med. Sci. Sports Exerc.* **1982**, *14*, 377–381. [CrossRef] [PubMed]
20. Cohen, J. A power primer. *Psychol. Bull.* **1992**, *112*, 155–159. [CrossRef]
21. Fye, H.; Pass, C.; Dickman, K.; Bredahl, E.; Eckerson, J.; Siedlik, J. The Effect of a Multi-Ingredient Pre-Workout Supplement on Time to Fatigue in NCAA Division I Cross-Country Athletes. *Nutrients* **2021**, *13*, 1823. [CrossRef]
22. Jeukendrup, A.E.; Thielen, J.J.; Wagenmakers, A.J.; Brouns, F.; Saris, W.H. Effect of medium-chain triacylglycerol and carbohydrate ingestion during exercise on substrate utilization and subsequent cycling performance. *Am. J. Clin. Nutr.* **1998**, *67*, 397–404. [CrossRef] [PubMed]
23. Cox, P.J.; Kirk, T.; Ashmore, T.; Willerton, K.; Evans, R.; Smith, A.; Murray, A.J.; Stubbs, B.; West, J.; McLure, S.W.; et al. Nutritional Ketosis Alters Fuel Preference and Thereby Endurance Performance in Athletes. *Cell Metab.* **2016**, *24*, 256–268. [CrossRef] [PubMed]
24. Holbrook, A.K.; Peterson, H.D.; Bianchi, S.A.; Macdonald, B.W.; Bredahl, E.C.; Belshan, M.; Siedlik, J.A. $CD4^+$ T cell activation and associated susceptibility to HIV-1 infection in vitro increased following acute resistance exercise in human subjects. *Physiol. Rep.* **2019**, *7*, e14234. [CrossRef]
25. Buchinsky, F.J.; Chadha, N.K. To P or Not to P: Backing Bayesian Statistics. *Otolaryngol. Head. Neck Surg.* **2017**, *157*, 915–918. [CrossRef] [PubMed]