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THE EFFECTS OF R-1,3-BUTANEDIOL WITH CARBOHYDRATE SUPPLEMENTATION ON CYCLING PERFORMANCE ABOVE THE LACTATE THRESHOLD

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THE EFFECTS OF R-1,3-BUTANEDIOL WITH CARBOHYDRATE SUPPLEMENTATION ON CYCLING PERFORMANCE ABOVE THE LACTATE THRESHOLD

A THESIS APPROVED FOR THE

DEPARTMENT OF HEALTH AND EXERCISE SCIENCE

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TABLE OF CONTENTS

LIST OF TABLES vi

LIST OF FIGURES vii

ABSTRACT viii

ACKNOWLEDGMENTS ix

CHAPTER 1: INTRODUCTION 1

1.1: Research Questions and Hypotheses 4

1.2: Delimitations 4

1.3: Limitations 5

1.4: Assumptions 5

1.5: Operational Definitions 5

CHAPTER 2: LITERATURE REVIEW 6

2.1: Introduction 6

2.2: Ketone Metabolism 6

2.3: Ketone Metabolism During Exercise 8

2.4: Exogenous Ketones in Cycling 9

2.5: Summary 15

CHAPTER 3: METHODS 15

3.1: Participants 15

3.2: Research Design 16

3.3: Study Protocol 16

3.4: Instrumentation 17

3.5: Data Analysis 18

3.6: Data Collection 19

CHAPTER 4: Results 19

4.1: Participant Characteristics 19

4.2: Time to Fatigue 20
4.3: Blood Lactate, Beta-hydroxybutyrate, and Glucose Pre and Post Exercise 21
4.4: Blood Lactate, Beta-hydroxybutyrate, and Glucose During Exercise 22
4.5: Gastrointestinal Responses 24
4.6: Profile of Mood States 24
4.7: Summary of Findings 25
CHAPTER 5: DISCUSSION 25
CONCLUSION 30
REFERENCES 31
APPENDIX A: IRB Approval 36
APPENDIX B: Consent Form 38
APPENDIX C: HIPAA Form 43
APPENDIX D: PAR-Q 46
APPENDIX E: POMS-B Questionnaire 52
APPENDIX F: GI Questionnaire 54
APPENDIX G: Table of Search Results 55

List of Tables

Table 1: Summary of studies reporting the effects of ketone supplementation on exercise. KET+CHO- ketone plus carbohydrate supplement; CHO- carbohydrate; KS- ketone supplement; βHB- beta-hydroxybutyrate; kg- kilograms; mg- milligrams; g-grams; BW- body weight; RER- respiratory exchange ratio.

Table 2: Participant characteristics. The values are the mean ± standard deviation. Cm- centimeters; Kg- kilograms; W- watts.

List of Figures

Figure 1: Individual TTF Measures. The dashed line represents the Mean ± Standard deviation for each condition. KET- ketone; CHO – carbohydrate; TTF – time to fatigue.

Figure 2: Blood Lactate Concentrations. Values are Means ± SD. KET- ketone; CHO- carbohydrate; Mm- millimoles; * significant difference in time (pre to post).

Figure 3: Blood Beta-hydroxybutyrate Concentrations. Values are Means ± SD. KET- ketone; CHO- carbohydrate; Mm- millimoles; *- significant time effect; **- significant condition effect; †- interaction effect.

Figure 4: Blood Glucose Concentrations. Values are Means ± SD. KET- ketone; CHO- carbohydrate; Mg/dL- milligrams per deciliter. ; * significant difference in time (pre to post).

ABSTRACT

Introduction: The purpose of this study was to examine the effects of R-1,3-Butanediol combined with carbohydrate supplementation on cycling performance above the lactate threshold. Exogenous ketones have gained attention as a potential benefit for exercise performance, serving as an alternative fuel source during exercise. **Methods**: A randomized, crossover design was performed in which eleven trained endurance athletes completed two experimental trials: ketone-plus-carbohydrate (KET+CHO) and a carbohydrate-only (CHO) condition. Participants consumed the beverage 30 minutes and immediately before exercise. Participants cycled at an intensity of 15% above their lactate threshold until volitional exhaustion on a cycle ergometer. Time to fatigue (TTF) served as the primary performance outcome variable. Physiological variables, including blood lactate, blood beta-hydroxybutyrate (βHB), and blood glucose, were measured before, during, and after exercise. **Results:** No significant differences were observed between conditions for TTF ($p = 0.59$). However, the percent difference in TTF was 21.1% greater in the KET+CHO condition compared to the CHO condition. Blood βHB concentration was elevated following ketone supplementation, confirming nutritional ketosis. No significant differences in blood lactate or blood glucose were observed between conditions. **Conclusions:** These findings suggest that R-1,3-Butanediol combined with carbohydrate supplementation does not significantly improve cycling performance above the lactate threshold in trained endurance athletes. Nevertheless, the observed increase in TTF may indicate a potential performance benefit that warrants further investigation with larger sample sizes, alternative dosing strategies, and other physiological measurements.

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CHAPTER 1: INTRODUCTION

Athletes continually seek ways to enhance their endurance, enabling them to perform for longer periods and maintain peak performance levels (Evans et al., 2022). The appreciation of carbohydrates and fats as fuel sources is widely accepted in endurance sports, and most research into the metabolic response to exercise has primarily focused on these fuel sources. An alternative fuel source to carbohydrates and fats is ketone bodies, primarily acetoacetate (AcAc), acetone, and beta-hydroxybutyrate (βHB). Ketone bodies are produced in the liver from free fatty acids in response to decreased carbohydrate availability, which is typically observed during fasting, starvation, or following a ketogenic diet (Evans et al., 2017). The reduction of glucose availability and the associated elevation in free fatty acids lead to the production of ketone bodies, which replace glucose as the primary fuel source for peripheral tissues such as the brain, heart, and skeletal muscle. In addition, ketone bodies are oxidized as a fuel source during exercise, are elevated during the post-recovery period, and their utilization is greater in exercise-trained skeletal muscle (Evans et al., 2017). Therefore, the metabolic actions of ketone bodies can influence fuel selection by reducing glucose utilization in peripheral tissues, exerting anti-lipolytic effects on adipose tissue, and decreasing proteolysis in skeletal muscle. Ketone bodies also function as signaling metabolites, with beta-hydroxybutyrate inhibiting histone deacetylases, which regulate the adaptive response to exercise in skeletal muscle (Evans et al., 2017).

In a postprandial state, blood ketone bodies are typically < 0.1mM and approximately 0.1-0.4mM because of an overnight fast. Following twenty-four hours of fasting, blood ketone levels are approximately 1.0mM, and after one week of fasting, they are around 5.0mM. In athletic contexts, the goal is to induce acute hyperketonemia exceeding 0.5 mM as a way to understand its potential metabolic effects on exercise without dietary restrictions (Evans et al.,

2017; Shaw et al., 2019). Based on some of the current understanding of ketones' influence on fuel selection as it relates to skeletal muscle, supplement companies have begun marketing exogenous forms of ketones, which are now commercially available and have even received FDA approval. These include medium-chain triglycerides (MCT), beta-hydroxybutyrate (βHB) salts and/or amino acids, esters, and racemic versions (Evans et al., 2017). Many studies have used these forms of ketone bodies to explore the dose-response relationship associated with them in athletic contexts.

The investigation on the potential metabolic effects of ketone supplementation on sports performance has shown that ketones can increase oxygen consumption (Shaw et al., 2019). Shaw and colleagues in 2019 measured beta-hydroxybutyrate levels, serum glucose, lactate, oxygen consumption, and carbon dioxide production during an 85-minute steady-state cycling followed by a 25-35-minute time trial. The study showed no changes in cardiorespiratory, metabolic, or performance measures, with only an increase in blood beta-hydroxybutyrate levels. However, the study observed increased oxygen consumption and carbon dioxide production after 20 minutes of steady-state cycling with the ingestion of ketone bodies. They reported that the highest peak of beta-hydroxybutyrate was recorded one hour after the time trial (Shaw et al., 2019). A similar study measuring the effects of 1,3-butanediol before a time trial in professional male cyclists found no performance benefits, nor any benefits to time trial performance. Similarly, beta-hydroxybutyrate levels were highest following the time trial (Leckey et al., 2017). On the contrary, one study examining the effects of ketone ingestion before exercise found that glucose levels were reduced, and the respiratory exchange ratio was higher than that of a placebo (Evans et al., 2018). Dearlove in 2021 reported an exercise efficiency increase by approximately 7% in

trained cyclists when blood beta-hydroxybutyrate was approximately 2mM (Dearlove et al., 2021).

Although ketone supplementation has shown positive and negative results, the investigation of ketone bodies with other supplementation has shown productive results. Ketone supplementation with carbohydrates increased oxygen consumption, decreased blood lactate and glucose concentrations, and decreased glycolytic intermediates in cycling approximately one to two hours at 45%-75% watt max (Cox et al., 2016). Measurements surrounding ketone supplementation during exercise are still being investigated. Many studies show differing results regarding the effects of exogenous ketones. What most of the studies have in common is that the supplementation occurs before a specific exercise test. Secondly, the duration of these exercise tests does not exceed two hours. Similarly, the exercise protocol does not consider the metabolic environment when testing. Mostly percentages of VO_{2max}, W_{max}, or through time-trial performances have been utilized to look at the effects of ketone supplementation on cycling performance (Cox et al., 2016; Evans et al., 2018; Leckey et al., 2017). Others have investigated the effects of ketone supplementation with consideration of the metabolic environment using the ventilatory threshold (McCarthy et al., 2021; O'Malley et al., 2017; Rodger et al., 2017; Shaw et al., 2019). However, none of these studies have used an exercise protocol over the ventilatory threshold. Only one study has examined the impact of exogenous ketones utilizing an exercise protocol that surpasses the lactate threshold. However, it is important to note that this did not involve steady-state exercise, and the threshold was set at 175% above for a short duration (Poffé, Robberechts, et al., 2021).

The significance of this study is to address gaps in the literature by investigating the combined effects of R-1,3-Butanediol and carbohydrate supplementation on cycling performance

during steady-state exercise above the lactate threshold. The intent is to provide insights into metabolic and performance responses beyond traditional exercise intensities. The findings could inform endurance athletes and coaches on nutritional strategies for sustaining performance during high-intensity efforts. The purpose of this study is to investigate the performance effects of a ketone supplement (R-1,3-Butanediol) combined with a carbohydrate supplement on cycling performance above the lactate threshold.

Research Questions and Hypotheses:

1. R1: Is there a difference in time to fatigue between ketone supplementation with carbohydrates versus carbohydrates only?
    a. H0: There is no difference in time to fatigue between ketone supplementation with carbohydrates versus carbohydrates only.
    b. H1: Time to fatigue is longer with ketone supplementation and carbohydrates than with carbohydrates only.
2. R2: Will there be a difference in blood lactate measures between the two trials?
    a. H0: The two trials have no difference in blood lactate measures.
    b. H1: Ketone supplementation with carbohydrates will have lower blood lactate measures than carbohydrates only.

The delimitations of the study include:

1. Trained endurance athletes ages 18-55 (>6 hours endurance training per week).
2. The sample is drawn from the University of Oklahoma, local cycling and running events in Oklahoma, and local bicycle and running shops.

The limitations of the study include:

1. Small sample size of approximately 15 participants.
2. Recruitment from Oklahoma-based resources.
3. Self-reported training volume and diet.

Assumptions:

1. Participants perform tests with maximal effort.
2. Participants truthfully report training volume and diet.
3. Participants follow the prescribed diet.

Operational definitions:

1. R-1,3-Butanediol- racemic precursor metabolized into beta-hydroxybutyrate (βHB), often used exogenously (Evans et al., 2022).
2. Time to task failure (TTF)- the duration an individual can sustain a particular exercise or task at a given intensity until the task can no longer be performed (Souron et al., 2022).
3. Lactate threshold (LT)- the highest work intensity where there is a balance between lactate production and removal (Brooks, 1986).
4. Exogenous ketones- ketone bodies ingested through supplements or foods (Evans et al., 2022).

CHAPTER 2: LITERATURE REVIEW

Introduction

Athletes, coaches, and scientists continuously explore methods to improve endurance, enabling performance sustainability for extended periods at optimal levels. Recognizing carbohydrates and fats as primary fuel sources in endurance sports is well established. Recently, using exogenous ketones or ketone supplementation as an alternative fuel source has become more common in endurance sports. What is the difference between R-1,3-butanediol (exogenous ketones) with carbohydrate and carbohydrate supplements only on time to task failure, blood lactate and glucose levels, and blood ketone bodies during a long-duration exercise test in trained cyclists? This chapter will focus on what ketones are and how they are metabolized, how ketones function as a fuel source during exercise, and how the body responds physiologically during endurance-based sports, specifically cycling. Search engines used for the literature review include: CINAHL, Medline, SPORTDiscus, and PubMed. Search terms utilized include exogenous ketones, ketone supplementation, exogenous ketones and cycling, ketone supplementation and cycling, exogenous ketones and exercise, ketone supplementation and exercise, and ketone metabolism.

Ketone Metabolism

The concentration of ketone bodies in the circulatory system signifies the equilibrium between the processes of ketogenesis and ketolysis. Ketogenesis involves a series of reactions beginning with acetyl-CoA (Ac-CoA and acetoacetyl-CoA (AcAc-CoA) and ending with the release of acetoacetate (AcAc). Some AcAc is transported, but most is reduced to beta-

hydroxybutyrate (βHB) through 3-hydroxybutyrate dehydrogenase (BDH) (Evans et al., 2017). Ketogenesis represents an adaptive physiological response that supplies the body with energy during prolonged periods of reduced carbohydrate intake. Consequently, ketone bodies are synthesized from fatty acids and ketogenic amino acids, including leucine, lysine, phenylalanine, isoleucine, tryptophan, and tyrosine. Ketolysis occurs in extra-hepatic tissues where βHB enters the mitochondrial matrix through MCT1-mediated transport and is re-oxidized to AcAc through BDH, which forms two acetyl-CoA molecules. The acetyl-CoA molecules are then integrated into the citric acid cycle to aid the production of ATP to fuel muscular work. Compared to lipids and glucose, ketones are metabolized faster because of a single enzymatic reaction that produces two acetyl-CoA molecules (Evans et al., 2017). The primary ketone bodies acetoacetate (AcAc), acetone, and beta-hydroxybutyrate (βHB) are produced during reduced carbohydrate availability with the associated elevation in free fatty acids. This in turn provides peripheral tissues such as the heart, brain, and skeletal muscles with fuel.

The metabolic effects of ketone bodies influence fuel selection by reducing glucose utilization in peripheral tissues, inhibiting lipolysis in adipose tissue, and decreasing protein breakdown in skeletal muscle. Ketone bodies also act as signaling metabolites, with beta-hydroxybutyrate inhibiting histone deacetylases, influencing the adaptive response to exercise in skeletal muscle (Evans et al., 2017). This commonly occurs during fasting, starvation, or adherence to a ketogenic diet. In a postprandial state, the concentration of blood ketone bodies is generally observed to be less than or equal to 0.1 mM, with values rising to approximately 0.1-0.4 mM following an overnight fast. After a fasting period of twenty-four hours, the concentration reaches approximately 1.0 mM, while a duration of one week of fasting results in a concentration of around 5.0 mM. Within athletic contexts, the objective is to induce acute

hyperketonemia, exceeding 0.5 mM, to elucidate its metabolic effects without dietary restrictions (Evans et al., 2017; Shaw et al., 2019).

The primary ketone esters investigated include R, S-1,3-butanediol acetoacetate diester (Kesl et al., 2016) and (R)-3-hydroxybutyl (R)-3-hydroxybutyrate ketone monoester (Clarke et al., 2012; Cox et al., 2016). These ketone esters have been shown to induce acute nutritional ketosis, with levels reaching 0.5 mM at 6 hours, as indicated by beta-hydroxybutyrate concentrations exceeding 1 mM (Clarke et al., 2012; Kesl et al., 2016). The dosage of the ketone monoester has been proposed at 573 mg per kilogram of body weight, with beta-hydroxybutyrate rising to approximately 3 mM at 10 minutes and approximately 6 mM 30 minutes after ingestion (Cox et al., 2016). Facilitating the attainment of nutritional ketosis without the impracticalities or potential health implications associated with fasting or strict adherence to a ketogenic/low-carbohydrate diet is essential when discussing ketone supplementation in athletic contexts.

Ketone Metabolism During Exercise

During exercise, ketone body removal into skeletal muscle increases up to fivefold (Balasse et al., 1978; Féry & Balasse, 1983, 1986). This is characterized by a reduction in ketone bodies after the onset of exercise, which is concomitantly associated with an increase in the oxidation of ketone bodies within skeletal muscle and an increased metabolic clearance rate (Balasse et al., 1978; Féry & Balasse, 1983, 1986). The metabolic clearance rate refers to the capacity of tissues to eliminate ketones from the bloodstream. During exercise, clearance rates can be used to indicate the capability of such activity to stimulate the working muscles' capacity to extract and utilize ketones (Féry & Balasse, 1983, 1986). The metabolism of ketone bodies during exercise is affected by various factors, including metabolic status, training status, and the intensity of the exercise. The most significant factor during exercise is the level of ketonemia,

which refers to a high concentration of ketones in the bloodstream, regardless of whether it is achieved endogenously or exogenously. Ketone metabolism via endogenous methods, such as fasting or following a carbohydrate-restricted diet, is negligible when examining performance benefits for highly trained endurance athletes who depend on carbohydrates and fats as fuel sources. Therefore, the investigation of achieving ketonemia through exogenous methods has become more prevalent. Commercially available exogenous ketones, whether in their free acid form or buffered with sodium, potassium, or calcium salts, have been ineffective at producing ketosis. Consequently, ketone esters have been developed to produce ketosis. Acute ingestion of these ketone esters, namely R, S-1,3 butanediol acetoacetate diester and (R)- 3-hydroxybutyl (R)-3- hydroxybutyrate monoester, can achieve ketosis of >1 mM beta-hydroxybutyrate (Evans et al., 2017). Therefore, achieving ketosis without carbohydrate restriction or fasting becomes more practical.

Exogenous Ketones in Cycling

Using exogenous ketones in conjunction with carbohydrates appears to exhibit greater potential as an ergogenic aid than using exogenous ketone esters in isolation. The use of ketone esters associated with intravenous glucose after glycogen depletion increases insulin levels, glucose uptake, and muscle glycogen synthesis post-exercise (Holdsworth et al., 2017), which offers a potential adaptive advantage in skeletal muscle for enhanced endurance capabilities. In a comparable context, delta efficiency, or the measure of how efficiently muscles are working when the workload is changed, was significantly elevated when employing solely ketone esters, in contrast to the control group, during periods of glycogen depletion (Dearlove et al., 2021).

In multiple studies by Cox et al., 2016, high-performance athletes were tested utilizing exogenous ketone ester, 573 mg/kg body weight, to comprehensively analyze the body's

response during ketosis and its impact on physical endurance by altering fuel competition for oxidative respiration. The first study utilized six male endurance athletes to determine the effects of steady-state cycling exercise on the clearance of blood and urine ketones. The study results show that the ketone oxidation rate increased from 0.35g/min at 40% W_{Max} to 0.5g/min at 75% W_{Max}, as well as reductions in ketone body concentrations as exercise intensity increases. Regarding high-performance endurance exercise, the study exclusively measured the athletes for 45 minutes. The second study used ten male athletes to examine the effects of exogenous ketones compared to the intake of carbohydrates or fats, 96% of their calories from each substrate, during a steady-state cycling exercise at 75% W_{Max} over one hour. The findings reveal significant differences in lactate concentrations among the three trials, with the ketone group recording the lowest amounts. The post-exercise analysis demonstrated reduced levels of glycolytic intermediates in the ketone group, indicating that exogenous ketones suppress glycolysis in skeletal muscle, explaining the lower lactate concentration (Cox et al., 2016). Considering this analysis, exogenous ketones may possess the capacity to support prolonged exercise durations; however, further examination is required regarding the duration of exercise performed in this study.

The third study investigated the effects of exogenous ketones in conjunction with carbohydrates on eight male athletes during the identical exercise protocol employed in the second study. Comparable results indicated reduced lactate concentrations after the exercise (Cox et al., 2016). During a two-hour exercise protocol at 70% VO_{2max}, the fourth study investigated the effects of exogenous ketones combined with carbohydrates on intramuscular fat and glycogen stores in seven male endurance athletes. The respiratory exchange ratios observed were significantly lower than those of the carbohydrate-only group despite no notable changes in

intramuscular fat or glycogen levels (Cox et al., 2016). The fifth and final study investigated the effect of exogenous ketones with carbohydrates on exercise performance in six male and two female endurance athletes. This consisted of one hour of steady-state cycling exercise at 75% W_{Max} followed by a 30-minute time trial with the ingestion of exogenous ketones and carbohydrates. In prior studies, lactate concentrations were observed to be approximately 1.5-2 mM lower when using ketones with carbohydrates when compared to the carbohydrate-only group. Additionally, the performance during the time trial demonstrated a significant improvement, characterized by an increased average distance covered (Cox et al., 2016). In contrast to the initial three studies, the final two more accurately simulated an endurance race, providing enhanced insights into the potential efficacy of exogenous ketones.

Nevertheless, other studies present diverse findings regarding the effects of ketone supplementation when only exogenous ketones are used. The exclusive consumption of ketone esters may increase the respiratory exchange ratio during physical exercise and reduce glucose concentrations, suggesting a potential enhancement in the oxidation of ketone bodies. However, there was no change in lactate concentrations, perceived exertion, or muscular efficiency. (Evans et al., 2018). In a study (Shaw et al., 2019), using R, S-1,3-butanediol (0.35g/kg), lactate and glucose concentrations remained consistent across trials, and no performance benefits were observed in each of the time trials. There was an increase in oxygen consumption and alterations in carbon dioxide production in the ketone ester group compared to the control group. The exercise protocol lasted less than two hours, as reported in other studies. Similarly, a study examining the impact of ketone diester 1,3-butanediol (2 x 250mg/kg) on endurance performance during a time trial yielded comparable results. The research demonstrated that ketone esters exhibited no enhancement in time trial performance in conjunction with

carbohydrate consumption (Leckey et al., 2017). However, this study administered the ketone diester prior to the exercise instead of during it, and the duration was limited to approximately one hour. With the exception of Shaw et al., 2019, the previous studies investigated the effects of exogenous ketones using exercise protocols at VO_{2max}, VO_{2peak}, W_{max}, or through time-trial performance. Although acceptable measures of endurance performance, these measures do not reflect the metabolic environment as accurately as the ventilatory or lactate threshold. In a study investigating the effects of a ketone salt (0.3 g/kg βHB) with 10 recreationally active males on a submaximal cycling exercise test at 30%, 60%, and 90% of their ventilatory threshold, followed by a 150kJ time-trial, findings showed the respiratory exchange ratio was lower in the ketone group compared to a placebo ($p < 0.001$). Other study results showed increased fat oxidation ($p = 0.02$) and decreased carbohydrate oxidation ($p = 0.005$) compared to a taste-matched placebo and a decrease in glucose concentrations in the ketone group (O'Malley et al., 2017). A similar study using ketone salts in a steady-state cycling test at 80% of the ventilatory threshold, followed by a 4-minute maximal cycling performance test, showed an increase in the respiratory exchange ratio during both the submaximal and maximal tests. VO_2 did not differ between the ketone group and the placebo group, but VO_2 did increase in the ketone group during the maximal cycling test (Rodger et al., 2017). One study has examined cycling exercise above the lactate threshold with exogenous ketones, but it was performed at 175% for a short duration (Poffé, Robberechts, et al., 2021).

Table 1. Summary of studies reporting the effects of ketone supplementation on exercise.

Author (date)	**Study Design**	**Participants**	**Protocol**	**Ketone supplement dose, and timing**	**Results**
Cox et al. 2016	Crossover design; KET+CHO vs. CHO alone	Highly trained athletes (n=8)	1 hour steady-state cycling at 75% W_{max} followed by 30 min time-trial	(R)-3-hydroxybutyrate-(R)-1,3-butanediol; 573 mg/kg/BW; 30 min before exercise and at 60 min of exercise	Improves time-trial performance in KET+CHO group; 411 ± 162 m further vs. CHO alone
O'Malley et al. 2017	Crossover design; KS vs. minimal calorie, taste-matched control	Healthy adults (n=10)	Incremental cycling exercise (5 min at 30%, 60%, and 80% power at ventilatory threshold followed by 150 kJ time-trial	0.3 g βHB kg/BW, 0.01 g potassium kg/BW and 0.01 g sodium kg/BW; 30 min before exercise	Time to completion was worse in KS condition (mean ± SD; KS, 711 ± 137 s; control, 665 ± 120 s)
Rodger et al. 2017	Crossover design; KE vs. calorie-free, tasted-matched control drink	Highly trained cyclists (n=12)	90 min at 70% of ventilatory threshold 2 followed by 4 min performance test	11.7 g βHB salt; 20 min prior to exercise and after 30 min of exercise	No difference in 4 min performance test
Leckey et al. 2017	Crossover design; KE vs. taste-matched control drink	International level cyclists (n=8) and highly train U23 cyclist (n=3)	31 km time-trial on cycle ergometer	1,3-butanediol acetoacetate diester; 250 mg/kg/BW; 30 min before and immediately before 20 min warm-up	KE consumption resulted in decreased average power (mean ± SEM; KE, 339 ± 37 W; PLAC, 352 ± 35 W)

Evans et al. 2018	Crossover design; KS vs. control (plain water)	Trained cyclists (n=19)	Incremental cycling exercise (8 min steps at 30%, 40%, 50%, 60%, 70%, and 80% of VO_2 peak	0.38 g/kg/BW βHB salts; 60 min and 15 min prior to exercise	Blood glucose was lower in KS condition, no difference in lactate concentration, and RER was higher during exercise following KS ingestion.
Dearlove et al. 2021	Crossover design; low-dose KS vs. high-dose KS vs. control	Trained athletes (n=6)	60 min cycling exercise with 20 min intervals at 25%, 50% and 75% max power output	Low-dose βHB ketone monoester (252 mg/kg/BW); high dose βHB ketone monoester (752 mg/kg/BW); 60 min before exercise	Delta efficiency during cycling exercise was higher in the low-dose KS (25.9% ± 2.1%) compared to control condition (24.1% ± 1.9%)
Shaw et al. 2019	Crossover design; KS vs. placebo	Trained male cyclists (n=9)	85 min steady-state cycling exercise followed by a 25-35 min time trial	R,S-1,3-butanediol; 0.35 g/kg/BW; 30 min before exercise and 60 min during exercise	No difference in time trial performance.

KET+CHO- ketone plus carbohydrate supplement; CHO- carbohydrate; KS- ketone supplement; βHB- beta-hydroxybutyrate; kg- kilograms; mg- milligrams; g-grams; BW- body weight; RER- respiratory exchange ratio.

Summary

Ketone supplementation, or the use of exogenous ketones, has gained significant prominence in athletic performance and, thereby, in academic research. The use of exogenous ketones has come with varying results. In certain instances, athletic performance may remain unchanged or even decline, with no alterations in lactate or glucose concentrations. Other studies have yielded results indicating a reduction in lactate and glucose concentration, potentially suggesting the suppression of glycolysis. It is generally acknowledged that ketone esters may facilitate enhanced oxygen consumption, increased carbon dioxide production, and greater oxidation of ketone bodies. Steady-state cycling exercise has yet to be explored above the ventilatory or lactate threshold. It is important to acknowledge that numerous endurance cycling events have a duration exceeding two hours and that most are performed above threshold. Therefore, examining the effects of ketone esters on steady-state cycling above the lactate threshold is to be explored because of the mixed metabolic environments utilized throughout previous literature.

CHAPTER 3: METHODS

Participants

In a study examining the effects of ketone supplementation with carbohydrates on eight male trained cyclists, time trial distance was further improved using ketone supplementation with carbohydrates compared to a carbohydrate-only group. The mean difference of the distance covered was 411 ± 162 meters (Cox et al., 2016). Using G*Power version 3.1, the effect size calculated from the mean difference and standard deviation of the mean difference was 2.54,

which indicates an adequate sample size of 5 participants. For a more conservative approach, an effect size of 1.25, half of the aforementioned effect size, provides us with a sample size of 9 with a power of 0.95 and an alpha of 0.05 when calculated using G*Power version 3.1. Therefore, eleven highly trained endurance athletes, males and females, were recruited through convenience sampling from the University of Oklahoma, Oklahoma cycling and running teams, and local cycling and running races in Oklahoma. Eligibility criteria were highly trained males and females, ages 18-55, who were currently undertaking greater than or equal to six hours of endurance training per week. Exclusion criteria included the following: cardiovascular disease, respiratory disease, gastrointestinal disease, metabolic disease, kidney disease, neurological disease, and pregnancy (Dearlove et al., 2021; Shaw et al., 2019).

Research Design

The research design is a repeated-measures, randomized, single-blind crossover design (Cox et al., 2016; Dearlove et al., 2021; Leckey et al., 2017; Shaw et al., 2019). There is a total of three visits, lasting approximately 2 hours and separated by at least 7 days.

Study Protocol

The protocol begins with a familiarization visit, during which participants completed a maximal graded exercise test. They were instructed to be at least 4 hours postabsorptive and not complete strenuous exercise within 24 hours of the initial visit, and each participant signed an informed consent form and an exercise history was obtained from training programs such as Strava, Garmin, etc. Participants' height and weight will be recorded. To determine VO_2 max and lactate threshold, a continuous incremental cycling test was performed on the Zwift bike. The test begins at 1 watt per kilogram of body weight and increases 0.5 watts per kilogram of body

weight every 3 minutes until two of the following were reached: volitional fatigue, inability to maintain cadence greater than 60 rpm, maximal heart rate within 10 bpm of age-predicted max heart rate, or respiratory exchange ratio greater than 1.10 (Beltz et al., 2016; Dearlove et al., 2021; Shaw et al., 2019). Lactate threshold is determined through fixed at 4 mmol. For the experimental visits, 48 hours before the tests, participants were instructed to record their dietary intake for the next two days. Twenty-four hours before the tests, participants were prescribed 6 g/kg of body weight of carbohydrates to standardize carbohydrate availability. On the test days, participants arrived in the morning at least 4 hours postabsorptive and had not completed strenuous exercise 24 hours before the visits, and completed a Profile of Mood States (POMS) questionnaire. Participants' height, weight, resting heart rate, lactate, glucose, and blood ketones were measured. They then consumed either a 30-gram carbohydrate (dextrose) beverage with zero-calorie peach flavoring or a 30-gram carbohydrate beverage with 5 grams of peach-flavored R-1,3-Butanediol (Ketone-IQ, Miami, Florida, USA) 30 minutes before the exercise protocol, immediately before, and every 30 minutes into the exercise protocol until termination. Participants' allocation was randomized, and they consumed the other corresponding beverage on the second visit. The exercise protocol is steady-state exercise at 15% above their lactate threshold until they can no longer hold a cadence of 60 rpm. Every 3 minutes, participants' RPE, heart rate, lactate, glucose, and blood ketones were recorded until 30 minutes post-exercise.

Instrumentation

Instrumentation includes a capillary lactate analyzer, Lactate Plus Meter (Nova Biomedical, Waltham, Massachusetts, USA). The Lactate Plus Meter demonstrates high reliability compared to laboratory lactate analyzers ($r = 0.91$) (Hart et al., 2013). A capillary blood sample was utilized and analyzed through the Precision-Xtra device (Abbott Laboratories,

Abingdon, United Kingdom) to measure blood beta-hydroxybutyrate and glucose. Compared to serum levels of beta-hydroxybutyrate and glucose, the reliability of capillary samples from the device is high, with strong correlations ($r = 0.99$, $p < 0.001$; $r = 0.86$, $p < 0.001$), respectively (Voulgari & Tentolouris, 2010). Cardiorespiratory measures were analyzed through a metabolic cart, Parvo Medics TrueOne 2400 (Parvo Medics, Murray, UT, USA). These instruments are imperative for measuring circulating blood ketones, lactate, glucose, and cardiovascular measures related to this study. Participants performed the protocol on the Zwift Ride connected to the Wahoo Kickr Core cycling trainer, which has been shown to have high reliability ($r = 1.00$) (Zadow et al., 2018), and it was used in conjunction with programming through Zwift. Zwift is a virtual training platform that integrates real-time power output, cadence, and heart rate from sensors to simulate cycling dynamics. Lactate threshold was determined through a fixed value of 4 mmol during the max effort, incremental cycling test.

Data Analysis

Data analysis was performed in IBM SPSS Statistics version 31. The significance level for all statistical tests was set at $\alpha = 0.05$. A two-way (trial x time) repeated-measures ANOVA with Bonferroni post hoc test was used for blood ketones, glucose, and lactate. The ANOVA was a 2x2 measuring values from pre to post. A paired t-test was performed to assess the difference in time to fatigue between the two conditions, the difference in blood measurements at the beginning of exercise and the first measure of exercise, and the difference in POMS scores between each visit. Effect sizes were calculated by dividing the absolute value of the standardized test statistics by the square root of the total sample size.

Potential threats to internal validity include experimental mortality due to the exercise duration, which is controlled by incentivizing participants to complete the study. Another threa

to internal validity is participant expectancy due to the difficulty of blinding the ketone supplement. This was minimized by introducing the non-ketone beverage with a zero-calorie, peach flavoring. There is a threat to external validity as this study only measures highly trained endurance individuals. However, the target population of the study is trained endurance athletes.

Data Collection

The lab's primary investigator and other trained graduate students aided in data collection. Data is confidential and stored in a locked filing cabinet in the lab. Online data collection is password protected.

CHAPTER 4: RESULTS

Participant Characteristics

Eleven trained endurance athletes (9 males, 2 females) completed all testing sessions. Participant characteristics are presented in Table 1. Mean ± SD age was 32.72 ± 7.84 years, height 173.68 ± 6.25 centimeters, and weight 77.17 ± 13.53 kilograms. Mean ± SD lactate threshold power (W) was 230.39 ± 44.92.

Table 2. Participant Characteristics

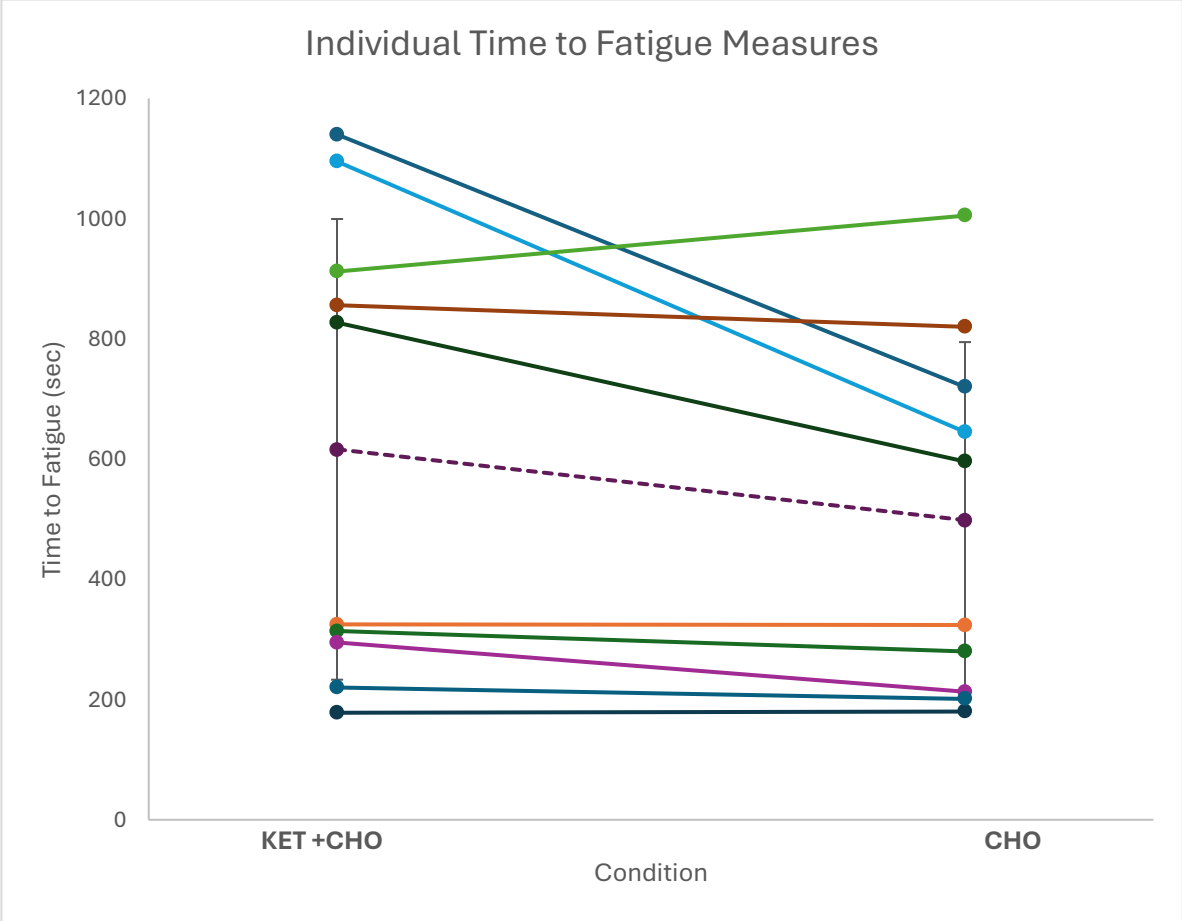
Variable	Whole cohort (*n* = 11)	Males (*n* = 9)	Females (*n* = 2)
Age (years)	32.72 ± 7.84	34.11 ± 7.96	26.50 ± 3.54
Height (cm)	173.68 ± 6.25	174.28 ± 6.75	171 ± 2.83
Weight (kg)	77.17 ± 13.53	69.72 ± 13.85	66.52 ± 4.12
Lactate threshold (W)	230.39 ± 44.92	232.14 ± 50.03	222.5 ± 2.12

Values are Mean ± Standard deviation. Cm- centimeters; Kg- kilograms; W- watts.

Time to Fatigue

One participant was excluded from this analysis due to outlying values deemed unrepresentative of the sample (greater than 3 standard deviations from the mean). The normality assumption was violated; the Wilcoxon Signed-Rank test was performed to assess differences in time to fatigue between the ketone-plus-carbohydrate supplement condition and the carbohydrate supplement condition. No significant difference in time to fatigue was observed between the ketone (616.2 ± 383.17 seconds) and the ketone-plus-carbohydrate (498.4 ± 296.20 seconds) conditions, $Z = -1.886$, $p = 0.59$, $r = 0.596$. The median pairwise difference was -69.0, 95% CI [-242.0, 0.50]. However, the mean time to fatigue in the ketone-plus-carbohydrate condition was 21.1% greater than in the carbohydrate condition. Individual participant responses are reported in Figure 1.

Figure 1. Individual TTF Measures



Dashed line represents the Mean ± Standard deviation for each condition. KET- ketone; CHO – carbohydrate; TTF -time to fatigue.

Blood Lactate, Beta-hydroxybutyrate, and Glucose Pre and Post Exercise

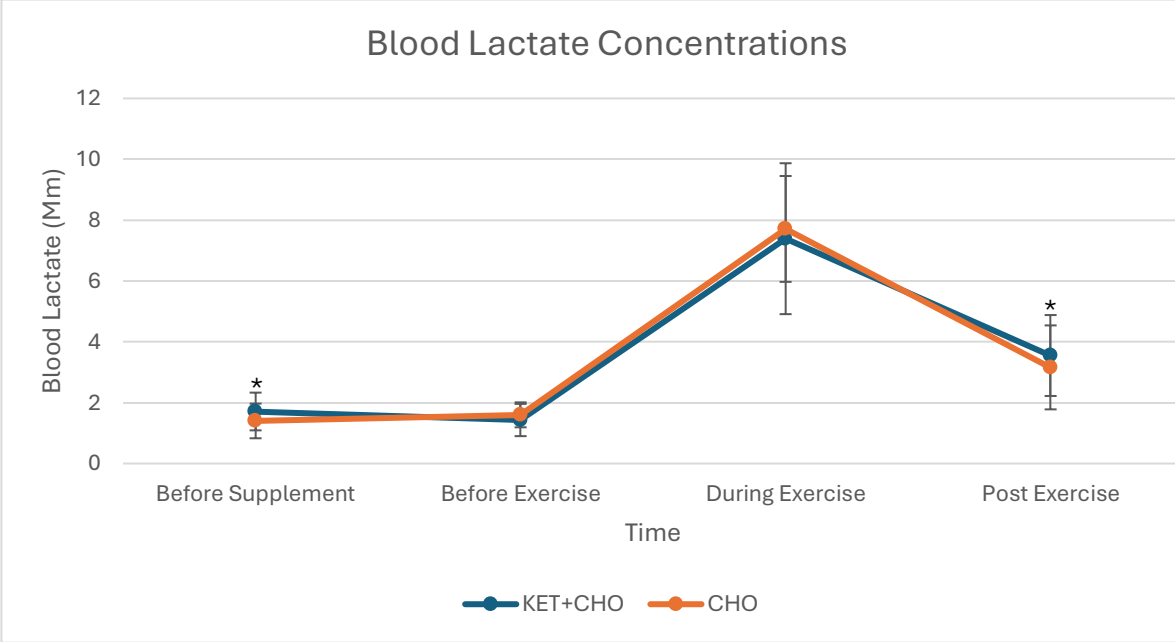
All participant data were included in this analysis. Lactate, beta-hydroxybutyrate, and glucose concentrations were analyzed using a two-way repeated measures ANOVA with factors of condition (KET+CHO vs. CHO) and time (Pre- and Post). There was a significant main effect of time for each variable: lactate ($F = 22.095$, $p < 0.001$, $\eta p^2 = 0.688$), beta-hydroxybutyrate ($F =$

55.956, $p < 0.001$, $\eta p^2 = 0.848$), and glucose (F = 14.271, $p = 0.004$, $\eta p^2 = 0.588$). Bonferroni post hoc comparisons show blood concentration values were lower pre-exercise than post-exercise ($p \leq 0.004$) There was no main effect of condition or a condition * time effect for lactate and glucose concentrations ($p \geq 0.138$). There was a significant effect of condition and condition * time effect on beta-hydroxybutyrate (F = 34.797, $p < 0.001$, $\eta p^2 = 0.777$; F = 48.708, $p < 0.001$, $\eta p^2 = 0.830$). Bonferroni post hoc analyses showed higher post-exercise beta-hydroxybutyrate concentrations in the ketone-plus-carbohydrate group ($p < 0.001$) compared with the carbohydrate-only group.

Blood Lactate, Beta-hydroxybutyrate, and Glucose During Exercise

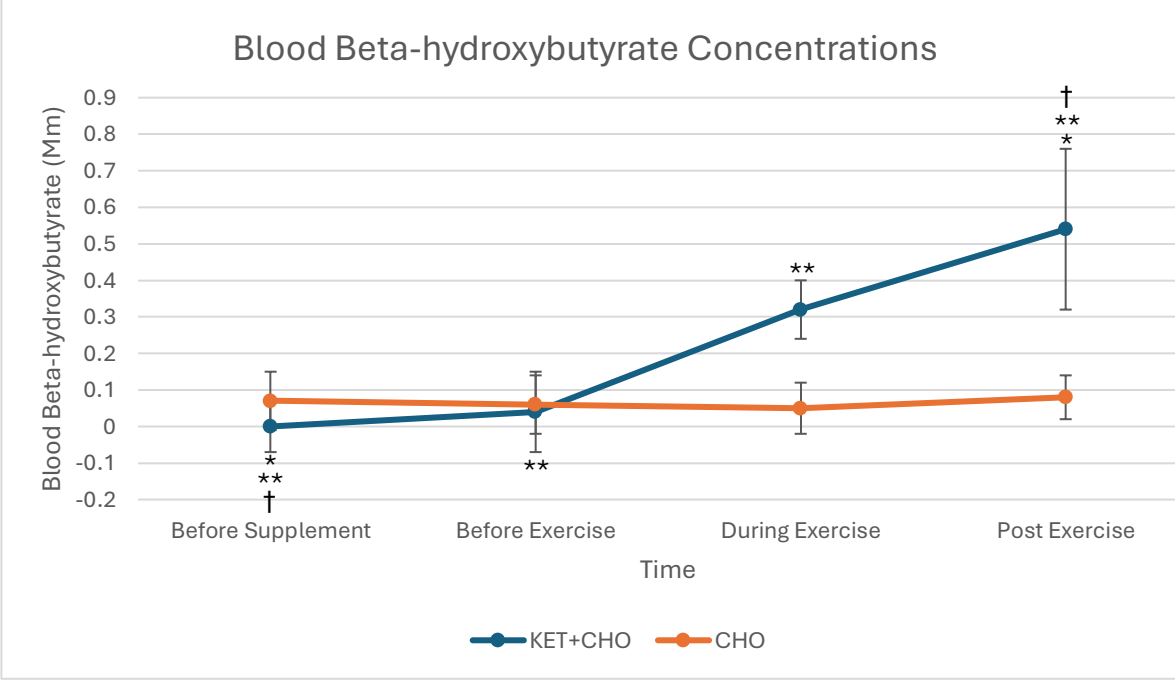
A paired sample t-test was performed to look at the mean differences of blood lactate, beta-hydroxybutyrate, and glucose at the first blood collection during exercise. There were no significant differences in blood lactate (t (10) = -0.522, $p = 0.613$) and glucose (t (10) = -0.508, $p = 0.622$). However, blood lactate was 4.24% higher in the carbohydrate condition compared to the ketone-plus-carbohydrate condition. Similarly, blood glucose was 4.78% higher in the carbohydrate condition compared to the ketone-plus-carbohydrate condition at the first measure of exercise. There was a significant difference in blood beta-hydroxybutyrate between the ketone-plus-carbohydrate and carbohydrate conditions (t (10) = 10.81, $p < 0.001$, $d = 3.26$). The percent difference between the two conditions for blood beta-hydroxybutyrate was 60.6%. Mean ± SD are reported in Figures 2, 3, and 4 along with pre- and post-measures.

Figure 2. Blood Lactate Concentrations



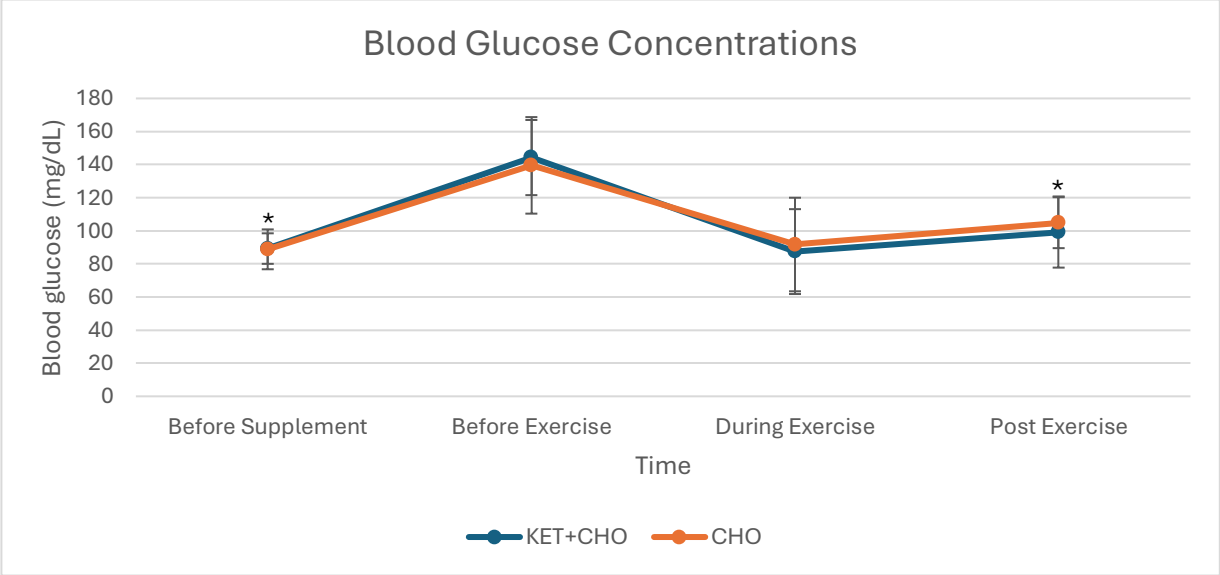
Values are Means ± SD. KET- ketone; CHO- carbohydrate; Mm- millimoles; * - significant difference in time (pre to post).

Figure 3. Blood Beta-hydroxybutyrate Concentrations



Values are Means ± SD. KET- ketone; CHO- carbohydrate; Mm- millimoles; *- significant time effect; **- significant condition effect; †- interaction effect.

Figure 4. Blood Glucose Concentrations.



Values are Means ± SD. KET- ketone; CHO- carbohydrate; Mg/dL- milligrams per deciliter; * - significant difference in time (pre to post).

Gastrointestinal Responses

One out of eleven participants reported symptoms of mild to moderate gastrointestinal distress in response to the ingestion of R-1,3-Butanediol. The reported symptoms were pyrosis (heartburn), dizziness, and headache. These symptoms occurred following the cessation of exercise. No other gastrointestinal symptoms were reported.

Profile of Mood States

A paired-samples t-test was performed to show any differences in the profile of mood states between the two experimental visits. There were no significant differences in mood states between the two visits (t (10 = 2.020, $p = 0.71$, $d = 0.609$).

Summary of Findings

There was no significant difference in time to fatigue between the ketone-plus-carbohydrate and carbohydrate conditions. Blood concentrations of lactate, beta-hydroxybutyrate, and glucose all had a main effect of time. Beta-hydroxybutyrate is the only measured variable that had a main effect of condition and a condition * time interaction. There were no significant mean differences in blood lactate and blood glucose between the two conditions during exercise, whereas beta-hydroxybutyrate showed a significant mean difference.

CHAPTER 5: DISCUSSION

The purpose of this study was to investigate the effects of R-1,3-Butanediol combined with carbohydrates on cycling performance above the lactate threshold. Specifically, this study examined whether ketone supplementation affected time to fatigue (TTF) and physiological responses, including blood beta-hydroxybutyrate (βHB), blood lactate, and blood glucose during high-intensity cycling exercise. The primary finding was that ketone supplementation, in tandem with carbohydrates, did not significantly affect time to fatigue. These findings suggest that acute R-1,3-Butanediol supplementation with carbohydrate supplementation did not provide an ergogenic benefit during cycling above the lactate threshold. However, the observed large effect size ($r = 0.596$) and a percent difference of 21.1% indicate that the magnitude of the difference between the two conditions may be practically meaningful despite the lack of statistical significance. Although ketone supplementation successfully elevated blood ketone concentrations, the increased availability of ketones may not have translated into improved exercise performance under the conditions of the present study.

Above the lactate threshold, ketone supplementation with carbohydrates did improve time to fatigue, as there is a 21.1% difference compared to the carbohydrate group. Although not statistically significant, it may provide meaningful insight into the practicality of the supplementation. As exercise intensity increases, reliance on carbohydrates as an energy source increases. Ketone supplementation can change the normal order of substrate utilization during exercise by increasing fat oxidation while providing an additional fuel source (Evans et al., 2017). Subsequently, the sparing of glycogen can be beneficial for long-duration exercise. An approximate 2% increase in cycling performance in highly trained athletes was found after consuming a ketone plus carbohydrate supplement, versus a carbohydrate-only supplement, before 90 minutes of cycling exercise (60 minutes at 75% W_{max}, followed by a 30-minute time trial)(Cox et al., 2016). However, ketosis may not be advantageous in situations that rely on anaerobic glycolysis or in those with high glycolytic flux for ATP production, such as high-intensity, short-duration exercise, as demonstrated in this study using an exercise protocol set at 15% above the lactate threshold. High glycolytic exercise may even be impaired if ketone oxidation impedes glycolysis (Cox et al., 2016). Considering this, an exercise intensity or duration threshold could exist at which ketone supplementation shifts from enhancing to hindering performance. Such evidence would explain why ketone supplementation had no effect on high-intensity intermittent running in male athletes (Evans & Egan, 2018). Similarly, exercise performance on an incremental cycling test to exhaustion showed no change in trained athletes (Dearlove et al., 2019). Protocols that include steady-state exercise with ketone supplementation may be advantageous for determining the metabolic effects of exogenous ketones; however, they seldom meet the demands of "real-world" athletic performance.

A study examining the effects of an acetoacetate (AcAc) diester combined with a carbohydrate supplement on time-trial performance in eleven internationally competitive male cyclists, with standardized pre-race nutrition and self-pacing, found that ketone-plus-carbohydrate supplementation reduced average power and time to completion (Leckey et al., 2017). Similarly, a 30-minute time trial followed by an all-out sprint (175% of lactate threshold) showed that ketone supplementation and ketone supplementation with bicarbonate impaired power output compared with a control group and a bicarbonate-only group (Poffé, Wyns, et al., 2021). These results contradict those reported by Cox et al. This could be due to a different ketone supplement or exercise protocol. While no statistically significant difference was observed between the two conditions, the ketone-plus-carbohydrate condition resulted in a 21.1% longer time to fatigue than the carbohydrate condition. It is possible that a physiological effect exists but was not detected within the present sample. Further work is required to demonstrate the ergogenic potential of ketone supplementation during intermittent exercise intensities, where energy-conversion benefits and carbohydrate conservation should be weighed against the potential impairment of high-intensity exercise.

The other hypothesis to be explored in the present study was that blood lactate levels would be lower in the ketone-plus-carbohydrate condition than in the carbohydrate condition. The findings showed no main effect of condition on lactate measures. A plausible explanation for this insignificance is that carbohydrate availability remained sufficient to sustain a similar rate of glycolysis, likely due to the exercise intensity and duration, resulting in comparable lactate production. Similar results were found in competitive male cyclists during a time trial, who ingested a ketone-plus-carbohydrate drink, with no change in lactate measures during exercise compared with a carbohydrate group. However, the study found that lactate measures were lower

following the time trial (Leckey et al., 2017). Conversely, when comparing ketone-plus-carbohydrate and carbohydrate-only during 60 minutes of steady-state cycling (75% W_{max}) followed by a 30-minute time trial, lactate concentrations were lower throughout exercise and following exercise (Cox et al., 2016). In the aforementioned studies, blood glucose concentrations were lower following ingestion of the ketone-plus-carbohydrate supplement and remained lower throughout exercise and post-exercise (Cox et al., 2016; Leckey et al., 2017).

The present study did not find any statistically significant change in blood glucose between conditions, nor any condition-time effect. Although the current study reached nutritional ketosis (0.5 mmol/L) without exceeding 1 mmol/L, other studies report higher blood ketone concentrations, suggesting metabolic effects during exercise. The above studies reported ketone concentrations of approximately 1-2 mmol/L, which had metabolic effects even in the presence of carbohydrate supplementation (Cox et al., 2016; Leckey et al., 2017). Proposed performance benefits with ketone supplementation may only be seen when blood ketone concentrations are in a range of 1-3 mmol/L (Cox et al., 2016; Egan & D'Agostino, 2016; Leckey et al., 2017). Furthermore, maximum beta-hydroxybutyrate concentrations are seen within 1.5-2.5 hours after consumption (Clarke et al., 2012). Ketone bodies have short half-lives, about 0.8- 3.1 hours. They are rapidly metabolized, and accumulation is not expected even after repeated consumption (Clarke et al., 2012). The absence of statistical significance of changes in blood lactate and blood glucose concentration between the two conditions may be explained by the amount of ketones ingested during the study, not allowing for blood ketone concentrations to reach 1 mmol/L. Participants in the current study ingested 10 grams of R-1,3-Butanediol, which was not normalized to their body weight. Another possible explanation for the lack of statistical significance is, as previously mentioned, the intensity and duration of exercise. The two

explanations in tandem may not have afforded any glycogen sparing, as glycolysis was likely the dominant metabolic pathway during the current exercise protocol.

Several limitations should be considered when interpreting the findings of this study. First, participants were trained endurance athletes, which may limit the generalizability of the findings to recreational active individuals and untrained individuals. Second, exercise intensity and duration performed by participants may not have been sufficient to understand the metabolic effects of ketone supplementation with carbohydrates, as glycolysis may have been the predominant metabolic pathway. Although examination of the data revealed a clear separation in individual responses, with some demonstrating improvements while others showed little to no improvement. Participants above the mean showed a longer time to fatigue using ketone supplementation compared to carbohydrates only. This suggests individual variability in baseline fitness, ketone metabolism, carbohydrate utilization, and general tolerability to the exercise protocol and supplement. Third, the amount of R-1,3-Butanediol may have been insufficient to spare muscle glycogen and increase time to fatigue. Fourth, not all participants provided dietary intake 48 hours prior to the experimental visits. Therefore, the prescription of 6g/kg body weight of carbohydrates to standardize glycogen stores is unknown in contributing to changes in metabolic concentrations. Furthermore, only blood lactate, beta-hydroxybutyrate, and glucose concentrations were assessed as indicators of metabolic response. Other potential variables, such as substrate oxidation, muscle glycogen oxidation, respiratory exchange ratio, and free fatty acids, were not measured and may provide insight into the potential benefits of ketone supplementation.

CONCLUSION

The purpose of this study was to investigate the effects of R-1,3-Butanediol combined with carbohydrate supplementation on cycling performance above the lactate threshold. Specifically, the study examined differences in time to fatigue, blood lactate concentration, beta-hydroxybutyrate, and glucose responses between a ketone-plus-carbohydrate condition and a carbohydrate-only condition in trained endurance athletes. The results indicated that the ketone-plus-carbohydrate supplement successfully elevated beta-hydroxybutyrate concentrations; however, no statistically significant differences were observed in time to fatigue, blood lactate, and blood glucose compared to carbohydrate supplementation alone. These findings suggest that acute ingestion of R-1,3-Butanediol with carbohydrates may not provide an ergogenic benefit during high-intensity cycling above the lactate threshold under the conditions examined in this study. Despite the lack of statistical significance, observations within the data may suggest that ketone-plus-carbohydrate supplementation may influence performance in some individuals. This study contributes to the growing body of literature examining ketone supplementation with carbohydrates and exercise performance by providing evidence from a trained endurance population performing exercise at intensities above the lactate threshold. Further research should investigate larger sample sizes, alternative dosing strategies, and additional physiological measures to further clarify the potential role of ketone-plus-carbohydrate supplementation on endurance performance. Collectively, the findings suggest that R-1,3-Butanediol with carbohydrate supplementation effectively increases beta-hydroxybutyrate concentrations; its acute use does not appear to enhance performance during high-intensity cycling above the lactate threshold.

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APPENDIX A: IRB Approval

The UNIVERSITY of OKLAHOMA

Institutional Review Board for the Protection of Human Subjects

Initial Submission – Board Approval

Date:	November 20, 2025	**IRB #:**	18836
To:	Rebecca Larson, PhD	**Meeting Date**:	11/10/2025
		Approval Date:	11/20/2025
		Expiration Date:	10/31/2026
Study Title:	The Effects of R-1,3-Butanediol with Carbohydrate Supplementation on Cycling Performance Above Lactate Threshold		
Study Status:	Active - Open | CR Req		

The University of Oklahoma Health Sciences Center's Institutional Review Board (IRB) reviewed the above-referenced research study at its regularly scheduled meeting and requested specific changes to the submission. On behalf of the IRB, I have verified that the specific changes requested by the convened IRB have been made and I grant final approval for this study.

Approval for this research is limited to the activities described in the approved protocol and application. In accordance with this approval, specific conditions for the conduct of this research are listed below, and informed consent from participants must be obtained as indicated.

Risk/Benefit Assessment: Research not involving greater than minimal risk.

Informed Consent Determination:
Informed consent and research privacy authorization must be obtained using the currently approved, stamped forms. You must retain all original, signed forms.

Continuing Review Determination:
As part of this approval, annual continuing review is required. You must promptly submit a Continuing Review/Final Closure Report Form and appropriate supporting documents to the IRB upon notification; approximately 60 days prior to the expiration date indicated above.

Principal Investigator Responsibilities:

- Conduct the research study in a manner consistent with the requirements of the IRB and federal regulations at 45 CFR 46 and/or 21 CFR 50 and 56.
- Request approval from the IRB prior to implementing any/all modifications.
- Promptly report to the IRB any harm experienced by a participant that is both unanticipated and related per IRB Policy.
- Maintain accurate and complete study records for evaluation by the HRPP quality improvement program and if applicable, inspection by regulatory agencies and/or the study sponsor.

The following are also required if applicable to this research study:

- You may *not begin your study* until the contract through Office of Research Administration (ORA) is finalized and signed as per OUHSC Institutional policy.
- If this study involves external sites requiring a reliance agreement for OUHSC to serve as IRB of record, submit a modification to add each non-OU site and non-OU collaborator to the application after a reliance agreement has been finalized.

1122 NE 13th Street, Suite CB202, Oklahoma City, OK 73117 (FWA00007961)

Study documents approved or accepted with this submission are listed below. If you have questions about this correspondence, contact the IRB at 405-271-2045 or irb@ouhsc.edu.

Sincerely,

Gene Hallford, PhD, Chair
Institutional Review Board

Study documents associated with this submission:

Study Document			
Title	Version #	Version Date	Outcome
HIPAA	Version 1.0	09/10/2025	Approved
Ketone Safety Information	Version 1.0	09/10/2025	Approved
Dr Smathers Letter	Version 1.0	09/10/2025	Noted
Flyer	Version 2.0	08/04/2025	Approved
GI Questionnaire	Version 1.0	07/14/2025	Approved
Oral Script	Version 1.0	07/14/2025	Approved
Email Script	Version 1.0	07/14/2025	Approved
POMS Questionnaire	Version 1.0	07/14/2025	Approved
Protocol	Version 1.1	09/10/2025	Approved
PARQ	Version 1.1	07/14/2025	Approved

Study Consent Form			
Title	Version #	Version Date	Outcome
Informed Consent	Version 1.5	08/04/2025	Approved

Information for Industry Sponsors: the columns titled Version Number and Version Date are specific to the electronic submission system (iRIS) and should not be confused with information included in the Document and/or Consent title(s).

APPENDIX B: Consent Form

Consent Form to Participate in a Research Study
University of Oklahoma Health Sciences Center (OUHSC)
University of Oklahoma Health and Exercise Department

Study Title: The Effects of R-1,3-Butanediol with Carbohydrate Supplementation on Cycling Performance Above the Lactate Threshold

Sponsor: Department of Health and Exercise Science, University of Oklahoma

Principal Investigator: Rebecca Larson Ph.D
Phone Number: Cole Connell B.Sc 405-628-3525

KEY INFORMATION ABOUT THE RESEARCH STUDY

You are being asked to participate in a research study. Research studies are voluntary and include only people who choose to take part. This consent form begins with a 'Key Information' section to provide important information to help you decide whether or not to participate in this study. More detailed information is provided after the key information. Please take your time, discuss this with family and friends, and ask the investigator and study team any questions you may have.

WHY HAVE I BEEN ASKED TO PARTICIPATE IN THIS STUDY?
You are being asked to participate in this research study because you are a student of the University of Oklahoma, local cycling and/or running club/team, or participate in local cycling and/or running events.

WHY IS THIS STUDY BEING DONE AND HOW LONG WILL IT LAST?
The purpose of this study is to compare the effects of ketone supplementation (R-1,3-Butanediol) with carbohydrate supplementation against carbohydrates only on you and other people who are trained cyclists and/or runners.

We think that you will be in the study for 2 hours on 3 days over 2 to 4 weeks.

WHAT WILL I BE ASKED TO DO IN THIS STUDY?
If you decide to participate in this study, you will be asked to cycle at maximal effort as well as at a certain threshold for approximately one hour. You will also be asked to provide a blood sample through a finger prick and be asked to consume a ketone supplement with carbohydrates or carbohydrates only.

WHY MIGHT I WANT TO PARTICIPATE IN THIS STUDY?
If you agree to take part in this study, there may or may not be a direct medical benefit to you. We hope that the information learned from this study will benefit you and other athletes in nutrition strategies for endurance exercise.

WHY MIGHT I NOT WANT TO PARTICIPATE IN THIS STUDY?
You may not want to participate in this study because it involves exercising at a maximal intensity for approximately one hour. Also, ketone supplementation and carbohydrate supplementation may cause gastrointestinal distress such as pain or cramping.

The researchers do not know all of the side effects that could happen. For a complete description of known risks, refer to the Detailed Information section of the consent form.

WHAT OTHER OPTIONS ARE THERE?
You may choose not to participate in this study.



HOW WILL PARTICIPATING IN THE STUDY AFFECT ME FINANCIALLY?
There is no additional cost to you if you participate in this study.

DETAILED INFORMATION ABOUT THE RESEARCH STUDY

The following pages of the consent form will provide you with more information about this study. Please take your time in reviewing this information and ask the investigator and study team any questions you may have.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?
About 15 people will take part in this study. All individuals will participate at this location.

WHAT IS THE STATUS OF THE R-1,3-Butanediol USED IN THIS STUDY?
R-1,3-Butanediol (Ketone IQ) is currently approved by the US Food and Drug Administration as a flavoring agent, and for specific applications like ready-to-drink sports beverages, nutrition beverages, meal replacement beverages, sports gels, energy drinks, and sports and nutrition bars. It is not FDA approved as used in this study.

WHAT IS INVOLVED IN THE STUDY?
You will be randomized to receive both R-1,3-Butanediol with carbohydrate supplementation one visit or carbohydrate on the other visit.

Randomization means that you are put in a group by chance. A computer program at the study sponsor will make this random assignment. You will receive the other supplement at a later visit.

If you take part in this study, you will have the following tests and procedures. These procedures are being done because you are in this study:

- A finger stick to get a drop of blood to measure lactate, glucose, and beta-hydroxybutyrate which is a ketone body that is produced from your liver.
- Lactate threshold test which includes cycling exercise with maximum effort and finger sticks to receive a drop of blood to measure your lactate.
- Use of a metabolic cart which includes putting a mask on that covers your nose and mouth to measure the contents of your breath to understand how well you use carbohydrates and fats.
- Use of cycle ergometer which involves a stationary bicycle that sets pre-determined resistance.
- The use of the MyFitnessPal application to record dietary intake.

WHAT ARE THE RISKS OF THE STUDY?
In addition to the risks described in the Key Information section, you may also be at risk for these side effects. You should discuss these with the researcher and/or your regular doctor. Many side effects go away shortly after the ketone supplementation is stopped.

Risks and side effects related to R-1,3-Butanediol we are studying include:

- Gastrointestinal distress
- Abdominal pain
- Abdominal cramping
- Nausea
- Vomiting
- Bloating

IRB APPROVED
IRB NUMBER: 18836
IRB APPROVAL DATE: 03/22/2026
IRB EXPIRATION DATE: 10/31/2026

- Dehydration
- Electrolyte imbalance
- Fatigue
- Muscle cramps

The likelihood of these risks occurring are low considering the amount of ketone supplement you will be taking.

REPRODUCTIVE RISKS FOR WOMEN AND MEN: If you are a female, you must not be and should not become pregnant nor breast-feed an infant while on this study. Taking the study drug(s) or undergoing a particular procedure or treatment involved in this study while you are pregnant or breastfeeding may involve risks to an embryo, fetus, or infant, including birth defects which are currently unforeseeable. In order to reduce your risk of pregnancy, you or your partner should use one or more of the acceptable methods of birth control listed below, regularly and consistently, while you are in this study.

Acceptable methods of birth control (continuing throughout the study and for 24 hours after the study) include:

- An approved oral contraceptive (birth control pill)
- Intra-uterine device (IUD) o Hormone implants
- Contraceptive injection (Depo-Provera)
- Barrier methods (diaphragm with spermicidal gel or condoms) o Transdermal contraceptives (birth control patch) o Vaginal contraception ring (birth control ring) o Sterilization (tubal ligation, hysterectomy or vasectomy)

If you are already using a method of birth control, you should check with the study doctor to make sure it is considered acceptable for this study. Certain drugs may interact with contraceptive agents and reduce their effectiveness; therefore, you should inform the study doctor of all medications (prescription and over-the-counter) that you are currently taking or begin taking during the study.

IN CASE OF PREGNANCY:
If you become pregnant or suspect that you are pregnant, or (for males) if you make someone pregnant during this study, you should immediately inform the study personnel. If you become pregnant or suspect that you are pregnant while on this study, tell the study doctor immediately; the study doctor will perform a pregnancy test. The study drug may be discontinued until the result of the pregnancy test is known. If pregnancy is confirmed, you may be withdrawn from the study. The study doctor will assist you in getting obstetrical care at your cost. The study doctor will follow the progress of your pregnancy and will request access to your and/or your infant's medical records for least eight weeks after delivery. Payment for all aspects of obstetrical, child, or related care will be your responsibility.

TO WHAT EXTENT WILL MY INFORMATION BE KEPT CONFIDENTIAL?
Efforts will be made to keep your personal information confidential. You will not be identifiable by name or description in any reports or publications about this study. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. You will be asked to sign a separate authorization form for use or sharing of your protected health information.

There are organizations outside the OUHSC that may inspect and/or copy your research records for quality assurance and data analysis. These organizations may include the US Food & Drug Administration and other regulatory agencies, the Department of Health and Exercise Science at the University of Oklahoma. The OUHSC Human Research Participant Program office, the OUHSC Institutional Review Board, OUHSC Office of Compliance, and other University administrative offices may also inspect and/or copy your research records for these purposes.



Storing and Sharing Your Information:
Any personal information that could identify you will be removed from your sample. Your sample will not be used for any future research studies.

Posting Study on ClinicalTrials.gov:
A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. However, this website will not include information that can identify you. At most, the website will include a summary of the study and results. You can search this website at any time.

CAN I WITHDRAW FROM THE STUDY?
You can stop participating in this study at any time. However, if you decide to stop participating in the study, we encourage you to talk to the researcher.

There may be circumstances under which your participation may be terminated by the investigator without your consent.

- You feel that it is in your medical best interest.
- New information becomes available.
- You fail to follow study requirements.

WHAT ARE MY RIGHTS AS A PARTICIPANT?
Taking part in this study is voluntary. You may choose not to participate. Refusal to participate will involve no penalty or loss of benefits to which you are otherwise entitled.

If you agree to participate and then decide against it, you can withdraw for any reason and leave the study at any time. You may discontinue your participation at any time without penalty or loss of benefits to which you are otherwise entitled.

We will provide you with any significant new findings developed during the course of the research that may affect your health, welfare, or willingness to continue your participation in this study.

You have the right to access the medical information that has been collected about you as a part of this research study. However, you may not have access to this medical information until the entire research study has completely finished. You consent to this temporary restriction.

WHOM DO I CALL IF I HAVE QUESTIONS, SUGGESTIONS, OR CONCERNS?
If you have questions, concerns, or complaints about the study or have a research related injury, contact Rebecca Larson Ph.D at 405-325-6325 or Cole Connell at 405-628-3525. Available 24 hours.

If you cannot reach the Investigator or wish to speak to someone other than the investigator and for questions about your rights as a research participant, contact the OUHSC Director, Office of Human Research Participant Protection at 405-271-2045.

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IRB NUMBER: 18836
IRB APPROVAL DATE: 03/22/2026
IRB EXPIRATION DATE: 10/31/2026

SIGNATURE:
By signing this form, you are agreeing to participate in this research study under the conditions described. You have not given up any of your legal rights or released any individual or entity from liability for negligence. You have been given an opportunity to ask questions. You will be given a copy of this consent document.

I agree to participate in this study:

_____	_____	_____
PARTICIPANT SIGNATURE (age ≥18)	**Printed Name**	**Date**
_____	_____	_____
SIGNATURE OF PERSON OBTAINING CONSENT	**Printed Name**	**Date**

IRB APPROVED
IRB NUMBER: 18836
IRB APPROVAL DATE: 03/22/2026
IRB EXPIRATION DATE: 10/31/2026

APPENDIX C: HIPAA Form

University of Oklahoma Health Sciences CenterResearch Privacy Form 1
PHI Research Authorization

AUTHORIZATION TO USE or SHARE
HEALTH INFORMATION[1] THAT IDENTIFIES YOU FOR RESEARCH
An Informed Consent Document for Research Participation may also be required.

Title of Research Project: **The Effects of R-1,3-Butanediol with Carbohydrate Supplementation on Cycling Performance Above Lactate Threshold**

Leader of Research Team: **Rebecca Larson PhD.**

Address: **1401 Asp Ave. Norman, OK 73019**

Phone Number**: 405-325-6325**

If you decide to sign this document, University of Oklahoma Health Sciences Center (OUHSC) researchers may use or share information that identifies you (protected health information) for their research. Protected health information will be called PHI in this document.

PHI To Be Used or Shared. Federal law requires that researchers get your permission (authorization) to use or share your PHI. If you give permission, the researchers may use or share with the people identified in this Authorization any PHI related to this research from your medical records and from any test results. Information used or shared may include all information relating to any tests, procedures, surveys, or interviews as outlined in the consent form; medical records and charts; name, address, telephone number, date of birth, race, government-issued identification numbers, and can include findings from questionnaires, anthropometric measures, and graded exercise tests.

Purposes for Using or Sharing PHI. If you give permission, the researchers will use your PHI to examine how ketone supplementation can impact performance, metabolic, and subjective measures during a graded exercise test.

Other Use and Sharing of PHI. If you give permission, the researchers may also use your PHI to develop new procedures or commercial products. They may share your PHI with other researchers, the research sponsor and its agents, the OUHSC Institutional Review Board, auditors and inspectors who check the research, and government agencies such as the Food and Drug Administration (FDA) and the Department of Health and Human Services (HHS), and when required by law. The researchers may also share your PHI with no one outside of the main research team.

Confidentiality. Although the researchers may report their findings in scientific journals or meetings, they will not identify you in their reports. The researchers will try to keep your information confidential, but confidentiality is not guaranteed. The law does not require everyone receiving the information covered by this document to keep it confidential, so they could release it to others, and federal law may no longer protect it.

[1] Protected Health Information includes all identifiable information relating to any aspect of an individual's health whether past, present or future, created or maintained by a Covered Entity.

Voluntary Choice. The choice to give OUHSC researchers permission to use or share your PHI for their research is voluntary. It is completely up to you. No one can force you to give permission. However, you must give permission for OUHSC researchers to use or share your PHI if you want to participate in the research and, if you cancel your authorization, you can no longer participate in this study.

Refusing to give permission will not affect your ability to get routine treatment or health care unrelated to this study from OUHSC.

Canceling Permission. If you give the OUHSC researchers permission to use or share your PHI, you have a right to cancel your permission whenever you want. However, canceling your permission will not apply to information that the researchers have already used, relied on, or shared, or to information necessary to maintain the reliability or integrity of this research.

End of Permission. Unless you cancel it, permission for OUHSC researchers to use or share your PHI for their research will never end.

Contacting OUHSC: You may find out if your PHI has been shared, get a copy of your PHI, or cancel your permission at any time by writing to:

Privacy Official University of Oklahoma Health Sciences Center PO Box 26901 Oklahoma City, OK 73190	or	Privacy Board University of Oklahoma Health Sciences Center PO Box 26901 Oklahoma City, OK 73190
If you have questions, call: (405) 271-2511	or	(405) 271-2045.

Access to Information. You have the right to access the medical information that has been collected about you as a part of this research study. However, you may not have access to this medical information until the entire research study is completely finished. You consent to this temporary restriction.

Giving Permission. By signing this form, you give OUHSC and OUHSC's researchers led by the Research Team Leader, permission to share your PHI for the research project listed at the top of this form.

Patient/Participant Name (Print): _____

_____ _____
Signature of Patient-Participant Date
(or Parent if participant is a minor)

Or

_____ _____
Signature of Legal Representative** Date

**If signed by a Legal Representative of the Patient-Participant, provide a description of the relationship to the Patient-Participant and the authority to act as Legal Representative:

_____

OUHSC may ask you to produce evidence of your relationship.

A signed copy of this form must be given to the Patient-Participant or the Legal Representative at the time this signed form is provided to the researcher or his representative.

APPENDIX D: PAR-Q

PAR-Q+

The Physical Activity Readiness Questionnaire for Everyone

The health benefits of regular physical activity are clear; more people should engage in physical activity every day of the week. Participating in physical activity is very safe for MOST people. This questionnaire will tell you whether it is necessary for you to seek further advice from your doctor OR a qualified exercise professional before becoming more physically active.

GENERAL HEALTH QUESTIONS

Please read the 7 questions below carefully and answer each one honestly: check YES or NO.	YES	NO
1) Has your doctor ever said that you have a heart condition OR high blood pressureO?	O	O
2) Do you feel pain in your chest at rest, during your daily activities of living, OR when you do physical activity?	O	O
3) Do you lose balance because of dizziness OR have you lost consciousness in the last 12 months? Please answer NO if your dizziness was associated with over-breathing (including during vigorous exercise).	O	O
4) Have you ever been diagnosed with another chronic medical condition (other than heart disease or high blood pressure)? PLEASE LIST CONDITION(S) HERE:	O	O
5) Are you currently taking prescribed medications for a chronic medical condition? PLEASE LIST CONDITION(S) AND MEDICATIONS HERE:	O	O
6) Do you currently have (or have had within the past 12 months) a bone, joint, or soft tissue (muscle, ligament, or tendon) problem that could be made worse by becoming more physically active? Please answer NO if you had a problem in the past, but it does not limit your current ability to be physically active. PLEASE LIST CONDITION(S) HERE:	O	O
7) Has your doctor ever said that you should only do medically supervised physical activity?	O	O

If you answered NO to all of the questions above, you are cleared for physical activity.
Please sign the PARTICIPANT DECLARATION. You do not need to complete Pages 2 and 3.

O Start becoming much more physically active - start slowly and build up gradually.
Follow Global Physical Activity Guidelines for your age (https://www.who.int/publications/i/item/978924001 51 28).

You may take part in a health and fitness appraisal.
If you are over the age of 45 yr and NOT accustomed to regular vigorous to maximal effort exercise, consult a qualified exercise professional before engaging in this intensity of exercise.

If you have any further questions, contact a qualified exercise professional.

If you answered YES to one or more of the questions above, COMPLETE PAGES 2 AND 3.

IRB APPROVED
IRB NUMBER: 18836
IRB APPROVAL DATE: 11/20/2025

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Delay becoming more active if:

You are currently experiencing a temporary illness, such as a cold or fever. It is best to wait until you feel better.

You are preanant. In this case, talk with your health care practitioner, physician, qualified exercise professional, and/or complete the ePARmed-)C+ at www.eparmedx.com before becoming more physically active.

D Your health changes. Answer the questions on Pages 2 and 3 of this document and/or talk to your health care practitioner, physician, or qualified exercase professional before proceeding with any physical activity program.

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01-1 1-2023

FOLLOW-UP QUESTIONS ABOUT YOUR MEDICAL CONDITION(S)

1. Do you have Arthrltls, Osteopomsls, or Back Problems?

If the above condition(s) is/are present, answer questions la-lc If NOO go to question [1]

la. Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? YESO [NO] O (Answer NO if you are not currently taking medications or other treatments)

1 b. Do you have joint problems causing pain, a recent fracture or fracture caused by osteoporosis or cancer, displaced vertebra (e.g., spondylolisthesis), and/or spondylolysis/pars defect (a crack in the bony ring on the YESO NOO back of the spinal column)?

Have you had steroid injections or taken steroid tablets regularly for more than 3 months? YESO [NO] O

2. Do you currently have Cancer of any kind?

If the above condition (s) is/are present, answer questions 2a-2b If NO go to question 3

2a. Does your cancer diagnosis include any of the following types: lung/bronchogenic, multiple myeloma (cancer of YES o NOO plasma cells), head, and/or neck?

2b. Are you currently receiving cancer therapy (such as chemotheraphy or radiotherapy)? YESO NOO

3. Do you have a Heart or Cardiovascular Condition? This includes Coronary Artery Disease, He ırt Failure, Diagnosed Abnormality of Heart Rhythm

If the above condition(s) is/are present, answer questions 3a-3d If NO go to question 4

Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? YESO NO O (Answer NO if you are not currently taking medications or other treatments)

3b. Do you have an irregular heart beat that requires medical management? (e.g., atrial fibrillation, premature ventricular contraction) YESO NO O

IRB APPROVED IRB NUMBER: 18836 IRB APPROVAL DATE: 1/30/2025 EXPIRATION DATE: 1/29/2026

PAR-Q+

3c. Do you have chronic heart failure? YESO NOO

3d. Do you have diagnosed coronary artery (cardiovascular) disease and have not participated in regular physical activity in the last 2 months? YESO NO O

4. Do you currently have High Blood Pressure?
If the above condition(s) is/are present, answer questions 4a-4b If NO go to question 5

4a. Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? YESO NO O (Answer NO if you are not currently taking medications or other treatments)

4b. (Answer YES if Do you have a you resting do not blood know pressure your resting equal to blood or greater pressure) than 1 60/90 mmHg with or without medication? YESO NO O

5. Do you have any Metabolic Conditions? This includes Type 1 Diabetes, Type 2 Diabetes, Pre-Diabetes
If the above condition(s) is/are present, answer questions 5a-5e If NO go to question 6

Do you often have difficulty controlling your blood sugar levels with foods, medications, or other physicianprescribed therapies? YESO NO O

Do you often suffer from signs and symptoms of low blood sugar (hypoglycemia) following exercise and/or during activities of daily living? Signs of hypoglycemia may include shakiness, nervousness, unusual YESO NO O irritability, abnormal sweating, dizziness or light-headedness, mental confusion, difficulty speaking, weakness, or sleepiness.

Do you have any signs or symptoms of diabetes complications such as heart or vascular disease and/or YESO NO O complications affecting your eyes, kidneys, OR the sensation in your toes and feet?

5d. Do you have other metabolic conditions (such as current pregnancy-related diabetes, chronic kidney YESO disease, or liver problems)? NOO

5e. Are you planning to engage in what for you is unusually high (or vigorous) intensity exercise in the near future? YESO NOO

6. Do you have any Mental Health Problems or Learning Diffculties? This incl udes Alzheimer's, Dementia, Depression, Anxiety Disorder, Eating Disorder, Psychotic Disorder, Intellectual Disability, Down Syndrome
If the above condition(s) is/are present, answer questions 6a-6b If NO go to question 7

6a. Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? YESO NOO (Answer NO if you are not currently taking medications or other treatments)

6b. Do you have Down Syndrome AND back problems affecting nerves or muscles? YESO NOO

IRB NUMBER: 18836
IRB APPROVAL DATE: 11/20/2025
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7. Do pu have a Disease? This includes Chronic Obstructive Pulmonary Disease, Asthma, Pulmonary High Blood Pressure

If the above condition(s) is/are present, answer questions 7a-7d If NO go to question 8

Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? NOO (Answer NO if you are not currently taking medications or other treatments)

7b. Has your doctor ever said your blood oxygen level is low at rest or during exercise and/or that you require NOO supplemental oxygen therapy? YES ☐

If asthmatic, do you currently have symptoms of chest tightness, wheezing, laboured breathing, consistent cough NOO (more than 2 days/week), or have you used your rescue medication more than twice in the last week?

Has your doctor ever said you have high blood pressure in the blood vessels of your lungs? NOO

8. Do pu have a Spinal Cord Injury? This includes Tetraplegia and Paraplegia

If the above condition(s) is/are present, answer questions 8a-8c If NO go to question 9

8a. Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? YESO NOO (Answer NO if you are not currently taking medications or other treatments)

8b.and/or Do you fainting?commonly exhibit low resting blood pressure significant enough to cause dizziness, light-headedness, YES ☐ NOO

8c. Has your physician indicated that you exhibit sudden bouts of high blood pressure (known as Autonomic Dysreflexia)? YESO NOO

9. Have you had a Strolæ? This includes Transient Ischemic Attack (TIA) or Cerebrovascular Event

If the above condition(s) is/are present, answer questions 9a-9c If NO O go to question 10 Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer NO if you are not currently taking medications or other treatments) YESO NOO

9b. Do you have any impairment in walking or mobility? YESO NOO

Have you experienced a stroke or impairment in nerves or muscles in the past 6 months? YESO NO O

10. Do you have any other medial condftlon not listed above or do you have two or more medial condftlons?

If you have other medical conditions, answer questions 1 Oa-10c If NO O read the Page 4 recommendations

Have you experienced a blackout, fainted, or lost consciousness as a result of a head injury within the last 1 2 months ORhave you had a diagnosed concussion within the last 1 2 months? YESO NOO

Do you have a medical condition that is not listed (such as epilepsy, neurological conditions, kidney problems)? YESO NO C)

IRB NUMBER: 18836
IRB APPROVAL DATE: 11/20/2025
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01-1 1-2023

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10c.Do you currently live with two or more medical conditions? YESO NOO

PLEASE USTYOUR MOICAL CONDITION(S) AND ANY RELATED MEDICATIONS HERE:

GO to Page 4 for recommendations about your current medical condition(s) and sign the PARTICIPANT DECLARATION,

3

/ you Ifyou are answeed ready NO to all more ofthe physically FOLLOW-UP questlons sign theHRTICIPANT%(pgs. 2-3) about Our medical condition, to become active - ECLARATION below:

It is advised that you consult a qualified exercise professional to help you develop a safe and effective physical activity plan to meet your health needs.

You are encouraaed to start slowly and build up gradually - 20 to 60 minutes of low to moderate intensity exercise, 3-5 days per weel< including aerobic and muscle strengthening exercises.

As you progress, you should aim to accumulate 1 50 minutes or more of moderate intensity physical activity per week.

If you are over the age of 45 yr and NOT accustomed to regular vigorous to maximal effort exercise, consult a qualified exercise professional before engaging in this intensity ot exercise.

O If you answered YES to one or more of the 6110w-up questions about your medical condition:

You should seek further information before becoming more physically active or engaging in a fitness appraisal. You should complete the specially designed online screening and exercise recommendations program - the ePARmed-X+ at www.eparmedxacom and/or visit a qualified exercise professional to work through the ePARmed-X+ and for further information.

If you answered **YES** to **one or more of the follow-up questions** about your medical condition:

You should seek further information before becoming more physically active or engaging in a fitness appraisal. You should complete the specially designed online screening and exercise recommendations program - the **ePARmed-X+ at www.eparmedx.com** and/or visit a qualified exercise professional to work through the ePARmed-X+ and for further information.

Delay becoming more active If:

You are currently experiencing a temporary illness, such as a cold or fever. It is best to wait until you feel better.

You are pregnant. In this case, talk to your health care practitioner, physician, qualified exercise professional, and/or complete the ePARmed-X+ at www.eparmedx.com before becoming more physically active.

Your health changes. Talk to your health care practitioner, physician, or qualified exercise professional before continuing with any physical activity program.

●You are encouraged to photocopy the PAR-Q+. You must use the entire questionnaire and NO changes are permitted. ● The authors, the PAR-Q+ Collaboration, partner organizations, and their agents assume no liability for persons who

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IRB NUMBER: 18836
IRB APPROVAL DATE: 11/20/2025
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01-1 1-2023

PAR-Q+

undertake physical activity and/or make use of the PAR-Q+ or ePARmed-X+. If in doubt after completing the questionnaire, consult your doctor prior to physical activity.

For more information, please contact

www.eparmedx.com
Email: eparmedx@gmail.com

The PAR-Q+ was created using the evidence-based AGREE process (1) by the PAR-Q+ Collaboration chaired by Dr. Darren E. R. Warburton with Dr. Norman Gledhill, Dr. Veronica Jamnikf and Dr. Donald C. McKenzie (2). Production of this document has been made possible through financial contributions from the Public Health Agency of Canada and the BC Ministry of Health Services.

Citation for PAR-Q+

Warburton DER, JamnikVK, Bredin SSD, and Gledhiil N on behalf of the PAR-Q+ Collaboration. The Physical Activity Readiness Questionnaire for Everyone (PAR-Q+) and Electronic Physical Activity of Health Services. The views expressed herein do not necessarily represent the views of the Readiness Medical Examination (ePARmed-X+). Health & Fitness Journal of Canada 201 1 .

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IRB NUMBER: 18836
IRB APPROVAL DATE: 11/20/2025
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APPENDIX E: POMS-B Questionnaire

I.D. Number: _____ **Session Number:** _____ **Date:** _____

POMS-B QUESTIONNAIRE

INSTRUCTIONS: Below is a list of words that describe feelings that people have. Please read each word carefully. Then circle the number that best describes:

☐ How you have been feeling during the PAST WEEK, INCLUDING TODAY.

☐ How you feel RIGHT NOW.

	Not At All	A Little	Moderately	Quite a Bit	Extremely
1. Tense	0	1	2	3	4
2. Angry	0	1	2	3	4
3. Worn out	0	1	2	3	4
4. Lively	0	1	2	3	4
5. Confused	0	1	2	3	4
6. Shaky	0	1	2	3	4
7. Sad	0	1	2	3	4
8. Active	0	1	2	3	4
9. Grouchy	0	1	2	3	4
10. Energetic	0	1	2	3	4
11. Unworthy	0	1	2	3	4
12. Uneasy	0	1	2	3	4
13. Fatigued	0	1	2	3	4
14. Annoyed	0	1	2	3	4
15. Discouraged	0	1	2	3	4

PLEASE ANSWER QUESTIONS ON OTHER SIDE



IRB NUMBER: 18836
IRB APPROVAL DATE: 11/20/2025

I.D. Number: _____ **Session Number:** _____ **Date:** _____

POMS-B QUESTIONNAIRE

INSTRUCTIONS: Below is a list of words that describe feelings that people have. Please read each word carefully. Then circle the number that best describes:

☐ How you have been feeling during the PAST WEEK, INCLUDING TODAY.

☐ How you have been feeling during the PAST 24 HOURS.

	Not At All	A Little	Moderately	Quite a Bit	Extremely
16. Nervous	0	1	2	3	4
17. Lonely	0	1	2	3	4
18. Muddled	0	1	2	3	4
19. Exhausted	0	1	2	3	4
20. Anxious	0	1	2	3	4
21. Gloomy	0	1	2	3	4
22. Sluggish	0	1	2	3	4
23. Weary	0	1	2	3	4
24. Bewildered	0	1	2	3	4
25. Furious	0	1	2	3	4
26. Efficient	0	1	2	3	4
27. Full of Pep	0	1	2	3	4
28. Bad-tempered	0	1	2	3	4
29. Forgetful	0	1	2	3	4
30. Vigorous	0	1	2	3	4



IRB NUMBER: 18836
IRB APPROVAL DATE: 11/20/2025

APPENDIX F: GI Questionnaire

ID:_____ Session:_____ Date:_____

GASTROINTESTINAL SYMPTOMS QUESTIONNAIRE

INSTRUCTIONS: Below is a list of gastrointestinal and systemic symptoms that can occur. Please read each carefully and then circle which best describes:

- How you have been feeling during the exercise protocol.
- How you are feeling RIGHT now.

	None	Very Mild	Mild	Moderate	Severe
1.Heartburn	0	1	2	3	4
2.Bloating	0	1	2	3	4
3.Abdominal Cramps	0	1	2	3	4
4.Abdominal Pain	0	1	2	3	4
5.Nausea	0	1	2	3	4
6.Vomiting	0	1	2	3	4
7.Flatulence	0	1	2	3	4
8.Dizziness	0	1	2	3	4
9.Headache	0	1	2	3	4
10.Lower back pain	0	1	2	3	4
11.Muscle Cramps	0	1	2	3	4

IRB NUMBER: 18836
IRB APPROVAL DATE: 11/20/2025

APPENDIX G: Table of Search Results

Table of Search Results

Search Engine	Search (S) terms	# Retrieved	# Met inclusion criteria	Article ID
CINAHL	S1 Exogenous ketones	17	2	
CINAHL	S2 Ketone supplementation	14	4	
CINAHL	S1 and S3 Cycling	2	0	
CINAHL	S2 and S3	3	2	
CINAHL	S1 and S4 Exercise	6	2	
CINAHL	S2 and S4	5	3	
CINAHL	S5 Ketone metabolism	41	1	
Medline	S1	30	5	
Medline	S2	15	5	
Medline	S1 and S3	5	2	
Medline	S2 and S3	4	2	
Medline	S5	69	0	
PubMed	S1 and S3	105	4	
PubMed	S2 and S3	80	2	
PubMed	S1 and S4	112	4	
PubMed	S2 and S4	134	2	
SPORTDiscus	S1 and S3 or S4	9	1	
SPORTDiscus	S2 and S3 or S4	6	2	
Manuel search	Balasse et al. (1978)		1	
	Clarke et al. (2012)		1	
	Cox et al. (2016)		1	
	Fery et al. (1983) (1986)		2	
	Leckey et al. (2017)		1	