Strategies to Augment Ketosis Variations of Ketone Metabolism

The Ohio State University IRB Approval June 5, 2023

IRB# 2022H0292

Informed Consent

The Ohio State University Consent to Participate in Research

Study Title:	**Strategies to Augment Ketosis: Variations in Ketone Metabolism (STAK- VKM)**
Principal Investigator:	**Jeff Volek PhD, R.D., Brianna Stubbs, DPhil**
Sponsor:	Department of Defense (DOD) BHB Therapeutics/ Juvenescence

- **This is a consent form for research participation.** It contains important information about this study and what to expect if you decide to participate. Please consider the information carefully. Feel free to discuss the study with your friends and family and to ask questions before making your decision whether or not to participate.
- **Your participation is voluntary.** You may refuse to participate in this study. If you decide to take part in the study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your usual benefits. Your decision will not affect your future relationship with The Ohio State University. If you are a student or employee at Ohio State, your decision will not affect your grades or employment status.
- **You may or may not benefit as a result of participating in this study.** Also, as explained below, your participation may result in unintended or harmful effects for you that may be minor or may be serious depending on the nature of the research.
- **You will be provided with any new information that develops during the study that may affect your decision whether or not to continue to participate.** If you decide to participate, you will be asked to sign this form and will receive a copy of the form. You are being asked to consider participating in this study for the reasons explained below.

Key Information About This Study

The following is a short summary to help you decide whether or not to be a part of this study. More detailed information is listed later in this form.

This study is intended to evaluate the effects of a ketone ester across various ages and metabolic health statuses. You will visit the test center for a consent and screening visit. In this visit, you will be asked to give consent to participate in this study, then you will be screened for eligibility to participate. Following this you will schedule one testing session. During this session you will come to the PAES Building at OSU in the morning, having had no food that day and take a Ketone drink. Various tests will be administered after ingestion. You will have blood draws to tell us more about your metabolic response to the product. We will take up to 90-100mL of blood, which is roughly ~ 6 tablespoons which is about 3/8 of a cup of blood. We will collect any urine you pass during the study test visit. You will be asked

to complete a survey at the beginning and end of each testing session. We expect the full visit experiment to last 4-5 hours. You will be monitored at all times by research staff.

1. Why is this study being done?

This study is being done to see how individuals respond to a ketone ester (KE) across different age groups and health statuses. With the ketogenic diet becoming more popular, research on ketones (a molecule created when fat is broken down in the body) has grown as well. It is now possible to increase blood levels of ketones by ingesting them directly instead of decreasing the carbohydrates, you eat or fasting for a long time. When ketones are consumed, they are quickly absorbed and increase blood levels of ketones, even in those who are not eating a very low-carbohydrate diet. Since they are so new, very little work has been done to show what level of ketone supplements are best for individual people. These findings will be used to help develop future research studies and help others to pick the right doses of ketone supplement.

2. How many people will take part in this study?

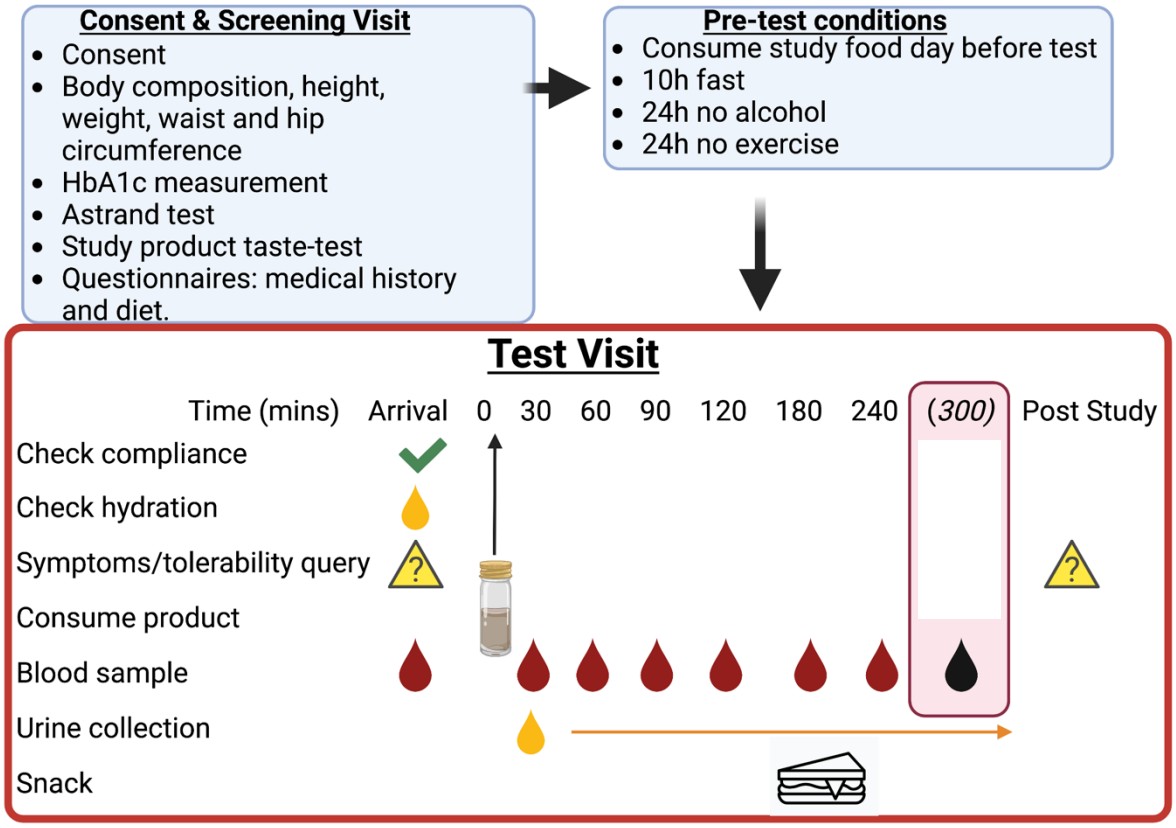
This study will be a multi-center study of up to 400 people of various ages and health status. We will enroll a large group representing a range of ages and metabolic health status. 300 participants will be recruited and tested at the Physical Activity and Education services facility at the Ohio State University, Columbus, OH, and 100 participants will be recruited and tested at the Buck Institute in Novato, California.

3. What will happen if I take part in this study?

First, you will visit the test center to discuss the study and to give your consent to participate. If you do consent to participate, you will be screened for your eligibility to participate, this will be based on:

1. Your answers to questionnaires including the online Automated Self-administered 24-hour Dietary Assessment Tool (ASA24®), and medical history questionnaire.
2. You will be asked to taste a small volume of ketone drink to screen for tolerance of the bitter tasting Ketone drink.
3. We will measure height, weight, hip & waist circumference, and body composition using bioelectrical impedance.
4. We will use a point of care Hba1c Blood monitor kit to assess Hba1c score. We will use both body composition and Hba1c score to ensure various metabolic statuses are represented in this study population.
5. You will complete a moderate effort bike test for 6 minutes. During this exercise you will be fitted with a heart rate monitor strap around your chest. You will begin pedaling at a low resistance and continue pedaling until the 6 minutes are over. This will tell us what your predicted ability to consume oxygen is. This will not be a part of your eligibility criteria. This will allow us to compare physical activity levels across the study participants.

If you meet all inclusion and none of the exclusion criteria then you are eligible for the study. If you are interested in participating for the completion of the study, then you will be scheduled to return to the study center for the testing visit at a time that is convenient for you. You will be given food to eat the day before the test visit.



Study overview:

Figure 2 | Study schematic, showing timeline for a study day.

Study Procedures

Study Day	Screening	Test Day
Visit to Study Center	X	X
Informed consent	X	
Medical intake questionnaire, diet assessment, body composition testing[1]	X	
Product enjoyment test	X	
HbA1c Measurement[2]	X	
6 Minute Bicycling Test[3]	X	
Distribute pre-test food	X	

Pretest assessment[4]		X
Hydration Status and Urine Collection[5]		X
Consume study product[6]		X
IV Cannulation and whole blood collection[7]		X
Fingerstick blood sample collection[8]		X
Symptoms / Tolerability assessment[9]		X

1. Body composition testing will include: body composition (measured using BIA), hip and Waist circumference, BMI, height, and weight.
2. HbA1c measurement will be taken by fingerstick.
3. 6 Minute bike testing will be completed.
4. Before starting the test day, you will be asked to confirm that they meet pre-test criteria, including: fasted >10h, no alcohol for 24h, no exercise for 24h and consumed the provided pre-test food.
5. Prior to drinking the Ketone drink, you will be asked to use the bathroom to completely empty your bladder. Then hydration status will be determined with urine specific gravity (USG), a device that tells us how hydrated you are, reporting <1.025. You will then only use the container we provide for you to empty your bladder until you finish testing.
6. You will drink the ketone drink. You will be provided with a choice of non-caffeinated, non-caloric beverage to remove the bitter taste of the Ketone drink.
7. IV cannula will be inserted at the start of the Test Day and removed at the end of the test Day, Blood samples will be collected according to the schedule in Figure 2. *Dependent*** A blood draw at 300min will only be required if your fingerstick ketone measurement at 240min is not similar to your baseline (0min). Cannula will be flushed with a small volume of saline after each draw.
8. Finger stick blood measurements will take place in order to show us your current ketone and glucose readings.
9. You will complete a Beverage Tolerability Questionnaire that will tell us if you have symptoms such as headache or stomach cramp before the ketone drink and at the end of the Test Day (**Appendix**)
10. After you have completed your testing day, you may leave the testing center.

Testing Visit: You will go to the test facility at PAES Building at OSU; on arrival you must meet the following criteria: no food for 10h, no alcohol or exercise for 24h, You will be asked to empty your bladder and collect a sample for the researchers to test your hydration. Then the researchers will insert an intravenous catheter into a vein and collect a blood sample; a small blood sample will also be collected from a finger stick. You will complete a symptoms/ tolerance questionnaire that asks about any symptoms you might be experiencing (i.e., headache stomach cramps). Then you will consume the study product. Blood samples will be collected from the IV catheter and from a fingerstick 30, 60, 90, 120, 180 and 240

minutes after you finish the study product. You will be asked to collect all urine that you pass during the study. After 240 minutes, you will be given a snack and be asked to complete a second symptoms/tolerance questionnaire. If your blood ketone concentrations are still higher than the start of the study at 240 minutes, you will stay for one further sample collection at 300 minutes post-study product before the study is stopped. If blood ketone concentrations are at/below the starting concentration at 240 minutes, the study is stopped. When the study stops, the IV catheter will be removed, and you will leave the test facility. All collected samples and data from this study will be coded to remove your name and maintain your privacy.

4. How long will I be in the study?

The duration of this study is expected to be about 1 week, which includes this consent meeting and screening, and one day of study testing. Total hours of commitment should be approximately 6 hours. This will include the 1-2 hour consent/screening session and the 4-5 hour testing session.

5. Can I stop being in the study?

You may leave the study at any time. If you decide to stop participating in the study, there will be no penalty to you, and you will not lose any benefits to which you are otherwise entitled. Your decision will not affect your future relationship with The Ohio State University.

6. What risks, side effects or discomforts can I expect from being in the study?

Ketone Supplements.

Drinking the supplement beverage could cause some people to have discomfort such as stomach cramps, nausea, vomiting or diarrhea. Additionally, this study is designed to assess palatability and tolerability of the supplement therefore it is possible that you may not like the taste of the product.

Blood Draws

Blood draws may cause discomfort at the skin puncture site and a small bruise may develop that may persist for several weeks. There is also a small possibility of an infection. In total we will take 90mL of blood, which is roughly ~ 6 tablespoons which is about 3/8 of a cup of blood. Blood draws will be done via an in-dwelling IV catheter and not separate "sticks" for each blood sample collection. Risks are minimized by using sterile disposable needles and gauze and the practice of aseptic (sterile) techniques during the blood draw.

Body Composition Testing

Bioelectrical composition devices are considered safe for most people. However, these should not be used if you have an electronic medical implant, such as a heart pacemaker or an implantable cardioverter defibrillator (ICD).

6 Minute Bicycling Test

Although this screening test requires minimal effort, you may feel slight discomfort in your legs after pedaling for 6 minutes. Risks are minimized by the resistance you pedal against being low.

7. What benefits can I expect from being in the study?

You will receive body composition analysis from your BIA Scan and will also be provided with your HbA1C numbers. Other than that, there are no potential benefits to being in the study. If there are unusual findings, we will consult with a physician.

8. What other choices do I have if I do not take part in the study?

You may choose not to participate without penalty or loss of benefits to which you are otherwise entitled.

9. Will my study-related information be kept confidential?

Efforts will be made to keep your study-related information confidential. However, there may be circumstances where this information must be released. For example, personal information regarding your participation in this study may be disclosed if required by state law.

Also, your records may be reviewed by the following groups (as applicable to the research):

- Office for Human Research Protections or other federal, state, or international regulatory agencies;
- U.S. Food and Drug Administration;
- The Ohio State University Institutional Review Board or Office of Responsible Research Practices;
- The Buck Institute for Research on Aging Human Subjects Research Committee
- The sponsor supporting the study, their agents or study monitors.

Authorized Ohio State University staff not involved in the study may be aware that you are participating in a research study and have access to your information.

10. Will my de-identified information and bio-specimens be used or shared for future research?

Yes, it/they may be used or shared with other researchers without your additional informed consent.

11. What are the costs of taking part in this study?

There is no cost to you or your insurance company for participating in this research study. There is no cost to you for the food you will be provided.

12. Will I be paid for taking part in this study?

By law, payments to subjects are considered taxable income. $50 will be received for completing the testing day. Payments will be provided in the form of check or pre-paid VISA card at the end of your testing day.

13. What happens if I am injured because I took part in this study?

If you suffer an injury from participating in this study, you should notify the researcher or study doctor immediately, who will determine if you should obtain medical treatment at The Ohio State University Wexner Medical Center.

The cost for this treatment will be billed to you or your medical or hospital insurance. The Ohio State University has no funds set aside for the payment of health care expenses for this study.

14. What are my rights if I take part in this study?

If you choose to participate in the study, you may discontinue participation at any time without penalty or loss of benefits. By signing this form, you do not give up any personal legal rights you may have as a participant in this study.

You will be provided with any new information that develops during the research that may affect your decision whether or not to continue participation in the study.

You may refuse to participate in this study without penalty or loss of benefits to which you are otherwise entitled.

An Institutional Review Board responsible for human subjects research at The Ohio State University reviewed this research project and found it to be acceptable, according to applicable state and federal regulations and University policies designed to protect the rights and welfare of research participants.

15. Who can answer my questions about the study?

For questions, concerns, or complaints about the study you may contact Drs Madison Kackley (kackley.1@osu.edu), 614-247-9650 or Brianna Stubbs (BStubbs@buckinstitute.org), 415-209-2000

For questions about your rights as a participant in this study or to discuss other study-related concerns or complaints with someone who is not part of the research team, you may contact the Office of Responsible Research Practices at 1-800-678-6251.

If you are injured as a result of participating in this study or for questions about a study-related injury, you may contact **Dr. Jeff Volek (volek.1@osu.edu) 614-688-1701**.

Signing the consent form

I have read (or someone has read to me) this form, and I am aware that I am being asked to participate in a research study. I have had the opportunity to ask questions and have had them answered to my satisfaction. I voluntarily agree to participate in this study.

I am not giving up any legal rights by signing this form. I will be given a copy of this form**.**

Printed name of participant	**Signature of participant**
	AM/PM
	Date and time
Printed name of person authorized to consent for participant (when applicable)	**Signature of person authorized to consent for participant (when applicable)**
	AM/PM
Relationship to the participant	**Date and time**

Investigator/Research Staff

I have explained the research to the participant or his/her representative before requesting the signature(s) above. There are no blanks in this document. A copy of this form has been given to the participant or his/her representative.

Printed name of person obtaining consent	**Signature of person obtaining consent**
	AM/PM
	Date and time

Witness(es) - *May be left blank if not required by the IRB*

Printed name of witness	**Signature of witness**
	AM/PM
	Date and time
Printed name of witness	**Signature of witness**
	AM/PM
	Date and time