PRINCIPAL INVESTIGATOR: Dr. Dimitrios Kapogiannis

STUDY TITLE: Ketone ester effects on biomarkers of brain metabolism and cognitive performance in cognitively intact adults ≥ 55 years old. A double-blinded randomized controlled clinical trial

STUDY SITE: National Institute on Aging (NIA) Clinical Research Unit, Medstar Harbor Hospital, Baltimore

Cohort: Standard, Adult DNA testing

Consent Version: October 29, 2024

WHO DO YOU CONTACT ABOUT THIS STUDY?

PI: Dr. Dimitrios Kapogiannis – 410-350-3953 - kapogiannisd@mail.nih.gov

Study Coordinator: Sarah Park – 410-350-7315 - sarah.park@nih.gov

KEY INFORMATION ABOUT THIS RESEARCH

This consent form describes a research study and is designed to help you decide if you would like to be a part of the research study.

You are being asked to take part in a research study at the National Institutes of Health (NIH). This section provides the information we believe is most helpful and important to you in making your decision about participating in this study. Additional information that may help you make a decision can be found in other sections of the document. Taking part in research at the NIH is your choice.

The purpose of this research study is to look at how a drink containing ketones affects the brain in people with normal cognitive function.

Glucose and ketones are the main energy fuel sources for the brain. Ketones are naturally produced in the body after many hours of fasting or while following a diet very low on carbohydrates/high fat (ketogenic diet).

We know that the brain of people with Alzheimer's disease, and to some lesser extent, the brain of older people or of people with Diabetes Mellitus or Metabolic Syndrome (a condition related to having resistance to the action of insulin, abnormal lipids and high blood pressure) cannot use glucose properly. On the other hand, brain can still make use of ketones, but they are not usually available, since prolonged fasting and low carbohydrate/high fat (ketogenic diets) are uncommon. A convenient way to increase ketones in the body is by taking a supplement drink containing ketones by mouth. Since ketones are the brain's preferred energy fuel, we believe that a ketone supplement could improve brain's function especially in people whose brains have difficulty using glucose.

If we find out that a ketone supplement increases ketone supply to the brain, and improves brain function and cognitive performance in people with Metabolic Syndrome and normal cognitive function, there will be a greater chance that it could also be helpful in Alzheimer's disease.

The study was completed with 50 participants. As you were already a participant in this study, we are asking you to come in for a single blood sample on an outpatient basis to obtain DNA. We want to collect this sample because it will allow us to see if genetic factors may affect response to the ketone ester supplement. This visit will take place at National Institute on Aging (NIA) Clinical Research Unit located at the Medstar Harbor Hospital in Baltimore.

The remaining document will now describe more about the research study. This information should be considered before you make your choice. Members of the study team will talk with you about the information described in this document. Some people have personal, religious, or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). Take the time needed to ask any questions and discuss this study with NIH staff, and with your family, friends, and personal health care providers.

IT IS YOUR CHOICE TO TAKE PART IN THE STUDY

You may choose not to take part in this study for any reason. If you join this study, you may change your mind and stop participating in the study at any time and for any reason. In either case, you will not lose any benefits to which you are otherwise entitled. However, to be seen at the NIH, you must be taking part in a study or are being considered for a study. If you do choose to leave the study, please inform your study team to ensure a safe withdrawal from the research.

WHY IS THIS STUDY BEING DONE?

The purpose of this research study is to test whether a drink that contains ketones (compared to a placebo drink that tastes similarly, provides the same amount of calories but does not contain ketones) can increase ketone supply to the brain and improve brain function. You have already taken part in the main part of the study.

The purpose of this visit is to collect a blood sample for DNA to see if genetic factors may affect the response to the Ketone Ester supplement.

WHAT WILL HAPPEN DURING THE STUDY?

If you decide to take part in this part of the study, you will be asked to come to the National Institute on Aging (NIA) Clinical Research Unit located at the Medstar Harbor Hospital in Baltimore for a research blood draw. No admission to the hospital will be required.

Visit 5:

During this visit, one of the study investigators or nurses will review this consent form with you and answer any questions you may have. After signing the consent form, blood will be drawn for genetic research purposes.

DNA is the genetic material in your blood and other samples.

All human beings share more than 99% of their DNA with each other. The tiny bit that is different is part of what makes each of us unique. Things like our hair color and eye color depend on the bits of our DNA that are different between human beings. We call these our DNA changes. These changes can also tell you about your health and how your body works. They can tell you about where your ancestors may be from. We are still learning about what role DNA plays in many parts of our lives.

DNA is passed from parents to kids. Half of your DNA came from your mom and half came from your dad. If you have kids, each of them will get half your DNA. In this way, your DNA also tells you about your family.

For this study, we will take up to 10ml (about 2 teaspoons) of blood. DNA will be extracted from this sample and analyzed. Specifically, we will test for certain genes, such as those related to the risk of Alzheimer's disease. However, we will not conduct whole Genome Sequencing (WGS) or whole Exome Sequencing (WES).

Your genetic information will be kept confidential to the maximum extent possible. The information of your genetic testing will be kept in a locked and secured manner at the NIH. Because the information we gather is generally preliminary and may need further study to fully understand its health relevance, we will not share your individual DNA results with you.

HOW LONG WILL THE STUDY TAKE?

Visit 5 will occur anytime after the completion of visit 4. This visit will take about 1 hour.

HOW MANY PEOPLE WILL PARTICIPATE IN THIS STUDY?

Up to 50 people who were previously enrolled may decide to have their blood collected.

WHAT ARE THE RISKS AND DISCOMFORTS OF BEING IN THE STUDY?

Risks/discomfort from:

- **Blood draws:** You may feel some pain and discomfort at the needle entry site where blood is drawn or where the intravenous line is inserted. There is a slight risk of bleeding or bruising around the site. Some people feel lightheaded or dizzy. There is a remote risk of fainting and infection after having blood drawn. To reduce the risk of injury because of a

fall, you will be closely monitored and asked about these symptoms before you are allowed to stand up. Clean aseptic technique will be used by experienced staff while drawing your blood.

- **Genetic testing:** The DNA analysis (genotyping, gene expression, and DNA Methylation studies) that will be done as part of this study is done for research purposes only. There may be no direct personal benefit to you from participating in this study, but you will be contributing to the effort to better understand the genetic disorder, which may improve the lives of others with this condition in the future.
  The primary risk associated with genetic testing in this study is the potential for a breach of confidentiality.
  Your genetic information will be kept confidential to the maximum extent possible. The results of your genetic testing will be kept in a locked and secured manner at the NIH. Genetic information about you will not be revealed to others, including your relatives, without your written permission. Similarly, you will not receive information about other family members. NIA researchers do not plan to provide you with the results of any laboratory investigations involving the use of your samples for genetic testing. There results will, in general, be preliminary. In many cases, additional research may be necessary to determine whether these results are meaningful in terms of health and disease.
- **Stored Samples:** The main risk associated with the use of stored samples is the possibility of a breach of confidentiality. Your stored sample information will be kept secure, and no research results will be entered into your medical record. Only authorized researchers will have access to your genetic information, and it will not be shared with any third party without your permission.

WHAT ARE THE BENEFITS OF BEING IN THE STUDY?

You will not benefit from being in this study.

Are there any potential benefits to others that might result from the study?

In the future, other people might benefit from this study because we will have a better understanding of how increased levels of ketones might affect the function of the brain. Importantly, if we find that this supplement improves memory and cognitive performance, in the future, we and/or other researchers might try to give this supplement to people with Alzheimer's Disease. This is very important since there is no current treatment for Alzheimer's.

WHAT OTHER OPTIONS ARE THERE FOR YOU?

Before you decide whether or not to continue in this study, we will discuss other options that are available to you. Instead of continuing in this study, you could choose not to participate.

DISCUSSION OF FINDINGS

New information about the study

If we find out any new information that may affect your choice to participate in this study, we will get in touch with you to explain what we have learned. This may be information we have

learned while doing this study here at the NIH or information we have learned from other scientists doing similar research in other places.

Return of research results

The results of this visit will not be shared with you.

EARLY WITHDRAWAL FROM THE STUDY

You may withdraw from the study at any time and for any reason without loss of benefits or privileges to which you are otherwise entitled. We can remove you from the study at any time if we believe that continuation of your participation in the study is not in your best medical interest, you have met an exclusion criterion, or you do not comply with study procedures.

STORAGE, SHARING AND FUTURE RESEARCH USING YOUR SPECIMENS AND DATA

Will your specimens or data be saved for use in other research studies?

As part of this study, we are obtaining specimens and data from you. We will remove all the identifiers, such as your name, date of birth, address, or medical record number and label your specimens and data with a code so that you cannot easily be identified. However, the code will be linked through a key to information that can identify you. We plan to store and use these specimens and data for studies other than the ones described in this consent form that are going on right now, as well as studies that may be conducted in the future. These studies may provide additional information that will be helpful in understanding the effects of ketones on brain metabolism, brain function and cognitive performance. This could include studies to develop other research tests, treatments, drugs, or devices, that may lead to development of a commercial product by the NIH and/or its research or commercial partners. There are no plans to provide financial compensation to you if this happens. Also, it is unlikely that we will learn anything from these studies that may directly benefit you.

I give permission for my coded specimens and data to be stored and used for future research as described above.

_____ Yes _____ No

Initials Initials

Will your specimens or data be shared for use in other research studies?

We may share your coded specimens and data with other researchers. If we do, while we will maintain the code key, we will not share it, so the other researchers will not be able to identify you. They may be doing research in areas similar to this research or in other unrelated areas. These researchers may be at NIH, other research centers and institutions, or commercial entities.

I give permission for my coded specimens and data to be shared with other researchers and used by these researchers for future research as described above.

_____ Yes _____ No

Initials Initials

If you change your mind and do not want us to store and use your specimens and data for future research, you should contact the research team member identified at the top of this document. We will do our best to comply with your request but cannot guarantee that we will always be able to destroy your specimens and data. For example, if some research with your specimens and data has already been completed, the information from that research may still be used. Also, for example, if the specimens and data have been shared already with other researchers, it might not be possible to withdraw them.

In addition to the planned use and sharing described above, we might remove all identifiers and codes from your specimens and data and use or share them with other researchers for future research at the NIH or other places. When we or the other researchers access your anonymized data, there will be no way to link the specimens or data back to you. We will not contact you to ask your permission or otherwise inform you before we do this. We might do this even if you answered "no" to the above questions. If we do this, we would not be able to remove your specimens or data to prevent their use in future research studies, even if you asked, because we will not be able to tell which are your specimens or data.

How Long Will Your Specimens and Data be Stored by the NIH?

Your specimens may be stored by the NIH until there is no remaining sample or the investigators decide to destroy the sample. However, your data may be retained and used for research purposes even after the specimen itself it no longer available.

Risks of Storage and Sharing of Specimens and Data

When we store your specimens and data, we take precautions to protect your information from others that should not have access to it. When we share your specimens and data, we will do everything we can to protect your identity, for example, when appropriate, we remove information that can identify you. Even with the safeguards we put in place, we cannot guarantee that your identity will never become known or someone may gain unauthorized access to your information. New methods may be created in the future that could make it possible to re-identify your specimens and data.

Can you change your mind about use and sharing for future research?

If you change your mind and do not want us to store and use your specimens and data for future studies, you should contact the study team. We will do our best to comply with your request but cannot guarantee that we will always be able to destroy your specimens and data. For example, if some research with your specimens and data is already complete, the information from that research may still be used. Also, if the specimens and data have been shared already, it might not be possible to withdraw them.

COMPENSATION, REIMBURSEMENT, AND PAYMENT

Will you receive compensation for participation in the study?

Participants will be paid $50 for this visit. You will also be given snacks and a meal ticket. This study does not offer reimbursement for, or payment of, travel, lodging or meals.

Will taking part in this research study cost you anything?

NIH does not bill health insurance companies or participants for any research or related clinical care that you receive at the NIH.

CONFLICT OF INTEREST (COI)

The National Institutes of Health (NIH) reviews NIH staff researchers at least yearly for conflicts of interest. This process is detailed in a COI Guide. You may ask your research team for a copy of the COI Guide or for more information. Members of the research team who do not work for NIH are expected to follow these guidelines or the guidelines of their home institution, but they do not need to report their personal finances to the NIH.

No NIH investigator involved in this study receives payments or other benefits from any company whose product is being tested.

CLINICAL TRIAL REGISTRATION AND RESULTS REPORTING

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

CONFIDENTIALITY PROTECTIONS PROVIDED IN THIS STUDY

Research records will be kept at the NIA in a locked room. Some data will be stored on secure computers. These are password protected and maintained on a secure server with access limited to authorized NIA staff members. All NIH investigators and NIA staff members who have access to these databases have the proper training on patient privacy as well as the required Human Subject Protection Training.

Social Security numbers are collected for the purpose of compensation. If you do not provide your social security number, you may still participate in the study, however, you may not be able to receive compensation.

Your samples will be stored in secured freezers at the NIA facility. The only information on the sample is your Study ID number. The key to the ID number will be kept in a separate secure area to which only the Clinical study staff have access.

Will your medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The NIH and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
- National Institutes of Health Intramural Institutional Review Board

NIH and researchers doing this study follow special laws and policies to keep your information as private as possible. However, your identity and information about being in this study may accidentally be seen by others.

In most cases, NIH will not share any identifiable information about you unless you say it is okay in writing. More information about sharing your information is below.

Information gathered for this study is protected under a Certificate of Confidentiality and the Privacy Act.

Certificate of Confidentiality

To help us protect your privacy, NIH has a Certificate of Confidentiality (Certificate). With this Certificate, researchers may not release or use information about you except in certain cases.

NIH researchers must not share information that may identify you in any legal proceedings, such as if a court requests it with a subpoena.

The Certificate does not protect your information when it:

1. is shared with people connected with the research. For example, information may be used for internal reviews by NIH; or
2. is required by law to be disclosed. For example, information may be shared with the FDA or with public health agencies.
3. is for other research if allowed by other regulations;
4. is shared with your consent.

Researchers may provide your information when you say it is okay. The Certificate does not keep you from sharing your own information.

The Certificate will not prevent telling authorities about harm to yourself or others. Examples are child abuse and neglect.

Privacy Act

The Privacy Act helps keep your NIH research information confidential. In some cases, it is different from the Certificate. This study's data will be stored under a NIH Privacy Act system numbered and named: 09-25-0200, Clinical, Basic and Population-based Research Studies of the National Institutes of Health (NIH). Sometimes the Privacy Act allows sharing your information without your permission. An example is if Congress requests it.

Information may also be shared for some research. It can be given to some federal and state agencies. It can be used for HIV partner notification, or for infectious disease, abuse, or neglect reports. It may be shared with tumor registries, or for quality or medical reviews. It may also be shared if NIH is involved in a lawsuit. However, NIH will only release information about you if allowed by both the Certificate and the Privacy Act. If you do not want to share your information with us, then you cannot participate in this study.

RESEARCH-RELATED INJURIES

NIA will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the NIH, NIA, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

PROBLEMS OR QUESTIONS

If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Dimitrios Kapogiannis, M.D. at kapogiannisd@mail.nih.gov or 410-350-3953 or the Study Coordinator, Sarah Park at 410-350-7315 or sarah.park@nih.gov. You may also call the Clinical Director at (410) 350-3922; the NIA Clinical Research Protocol Office at (410) 350-3947, or the NIH Office of IRB Operations at 301-402-3713, if you have a research-related complaint or concern.

CONSENT DOCUMENT

Please keep a copy of this document in case you want to read it again.

Adult Research Participant: I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I consent to participate in this study.

Signature of Research Participant	Print Name of Research Participant	Date

Investigator:

Signature of Investigator	Print Name of Investigator	Date