Title: The Interaction Between Diabetes and Estradiol on Human Brain Metabolism in Postmenopausal Women
Date: 4/19/2021
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Wake Forest®
School of Medicine

Section of Gerontology and Geriatric Medicine

FEMALE ESTROGEN MENOPAUSE MIND and ENERGY (FEMME): The interaction between diabetes and estradiol on human brain metabolism in postmenopausal women

Informed Consent Form to Participate in Research
Christina Hugenschmidt, PhD, Principal Investigator

SUMMARY

You are invited to participate in a research study. The purpose of this research is to better understand whether diabetes may affect the way your brain uses sugars and fats for energy in the presence of estrogen. We think this information may be helpful to people in the long-term in understanding how lifestyle factors such as diabetes and using hormone therapy can affect brain health in aging. You are invited to be in this study because you are a postmenopausal woman aged 60-80 either with or without type 2 diabetes. Your participation in this research will involve 6 visits and last about 3 to 4 months.

Participation in this study will involve at least 6 study visits at Wake Forest Baptist Medical Center and administration of 0.075 mg/day of transdermal-estradiol via a Climara patch for 8 weeks. During the study you will receive two MRI scans and two PET scans. All research studies involve some risks. Some risks involved in this study are side effects of estrogen administration (such as breast tenderness, spotting, or menstrual bleeding) and exposure to radiation (that is within accepted limits). There is no expectation that you will benefit directly from this study.

Your participation in this study is voluntary. You do not have to participate in this study if you do not want to. You will not lose any services, benefits, or rights you would normally have if you choose not to participate.

The remainder of this form contains a more complete description of this study. Please read this description carefully. You can ask any questions if you need help deciding whether to join the study. The person in charge of this study is Christina Hugenschmidt, PhD. If you have questions, suggestions, or concerns regarding this study or you want to withdraw from the study her contact information is:

Phone: [redacted]
Email: [redacted]

If you have any questions, suggestions or concerns about your rights as a volunteer in this research, contact the Institutional Review Board at [redacted] or the Research Subject Advocate at Wake Forest at [redacted].

WFU School of Medicine
Institutional Review Board
IRB Number: IRB00049740
Meeting Date Approved 4/19/2021
Version Valid Until: 8/12/2021

INTRODUCTION

You are invited to be in a research study. Research studies are designed to gain scientific knowledge that may help other people in the future. You are being asked to take part in this study because you are a postmenopausal woman aged 60-80 either with or without type 2 diabetes. Your participation is voluntary. Please take your time deciding whether you wish to participate. Ask your study doctor or the study staff to explain any words or information contained in this informed consent document that you do not understand. You may also discuss the study with your friends and family.

WHY IS THIS STUDY BEING DONE?

Research shows that type 2 diabetes is a risk factor for dementia that may affect women differently than men. Research also shows that type 2 diabetes status may interact with estrogen levels in the body to change the way that the brain uses sugars and fats for energy. Long-term changes in the way the brain uses sugars and fats may be one way that diabetes increases the risk for dementia. The purpose of this research study is to better understand the interaction between diabetes and estrogen on the brain in postmenopausal women.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

A total of 20 postmenopausal women, 10 with type 2 diabetes and 10 without, will participate in this study. In order to enroll the 20 women, we may have to screen as many as 200 individuals as some will not qualify.

WHAT IS INVOLVED IN THE STUDY?

You will be asked to complete at least 6 study visits at Wake Forest Baptist Medical Center. You will be administered 0.075 mg/day of transdermal estradiol via a Climara patch for 8 weeks. The Climara patch is FDA approved for the treatment of some symptoms of menopause.

Description of the Study Visits.

Screening Visit (SV): This visit will occur between 0 and 3 months prior to the beginning of the intervention and will take approximately 3 hours. Here we will determine your eligibility to enroll in the study. During this visit we will we ask you to:

- Read and sign a written informed consent;
- Have your height, weight, and blood pressure measured;
- Complete a fasting blood draw where you will have approximately 1 tablespoon of blood withdrawn from a vein to check the chemical levels in your blood and cholesterol;
- If you are non-diabetic, complete an oral glucose tolerance test (OGTT) to confirm non-diabetic status;
- Eat a healthy snack;
- Complete demographic and contact information forms;
- Complete a brief test of your memory and thinking skills;
- Review current medications and medical history, including radiation exposure;
- Review your medical record to confirm no evidence of potential contraindications to participate.

Study Visit 1 (V1): This visit will take place 0 to 3 months after your screening visit and will last approximately 2 hours. During this visit we will ask you to:

- Complete a fasting blood draw where you will have approximately 1.5 tablespoons of blood withdrawn from a vein. We use information from the blood to look at measures of blood sugar, fats, cortisol and hormones in the blood. Approximately 1 teaspoon of the total 1.5 tablespoons of blood will be stored and used for future research;
- Eat a healthy snack;
- Complete a set of memory and thinking tests;
- Have a 30 minute Magnetic Resonance Imaging (MRI) Scan of your brain. You will lie on a table and be placed inside a large device that will take pictures of your head using magnetic fields rather than radiation, such as x-rays. The study will require that you remain in the testing room for 30 minutes. Prior to having the MRI exam, you will be asked medical history questions, including whether you 1) have metal fragments or clips in your eyes, brain or spinal cord; 2) have a pacemaker, artificial heart valve, ear implant, or spinal cord stimulator; or 3) have had prior surgery for an aneurysm (bulging of a large blood vessel due to weakness of its wall) in your body or head.

Study Visit 2 (V2): This visit will take place 1-30 days after Study Visit 1 and will last approximately 3 hours. You will come to the PET Center having fasted for 6-7 hours. During this visit you will:

- Have a PET scan of your brain. Before the PET scan begins, a needle (or IV) will be inserted into a vein in your arm, and a small amount of the imaging agent will be injected. You will be placed in the PET scanner where you will need to lie still on a table with your head inside a large doughnut shaped machine. The table will move and the machine will make noises as the pictures are taken. After the scans are finished, you will be asked to drink fluids and empty your bladder.
- Have blood collected from the IV in your arm at various time intervals during the scan. Throughout the entire process a total of approximately 2 tablespoons of blood will be collected.
- Eat a healthy snack.
- Be given an 8 week supply of Climara estrogen patches with written and verbal instructions for applying and changing them weekly.
- Begin receiving weekly phone calls from the study coordinator who will be checking on your overall health status while you are in the study.

Study Visit 3 (V3): This visit will take place 2-4 days after you apply your second estrogen patch. During this visit you will be asked to:

- Have a blood draw where you will have approximately 1/4 of a teaspoon of blood drawn to assess your estrogen levels; if your levels are less than or more than the target range, the study physician will determine if the dosage on your patch needs to be adjusted and more blood draws may be necessary later on. A portion of the blood drawn at this visit will be used for studying your genetic information.

Study Visit 4 (V4): This visit will take place during week 8 of estrogen administration. You will come to the PET Center having fasted for 6-7 hours. During this visit you will:

- Repeat the PET Scan of your brain as was done at Study Visit 2. Throughout the entire process a total of approximately 2 tablespoons of blood will be collected.
- Eat a healthy snack.

Study Visit 5 (V5): This visit will also take place during week 8 of estrogen administration. During this visit you will:

- Complete a fasting blood draw where you will have approximately 1.5 tablespoons of blood withdrawn from a vein. We use information from the blood to look at measures of blood sugar, fats, cortisol and hormones in the blood. Approximately 1 teaspoon of the total 1.5 tablespoons of blood will be stored and used for future research;
- Eat a healthy snack;
- Complete a set of memory and thinking tests;
- Remove the estrogen patch;
- Repeat a 30 minute MRI scan.

The total amount of blood withdrawn during the entire study will be approximately 8 tablespoons.

We can send copies of your test results to your personal physician if you would like. If you do not wish to have any of your medical information sent to your physician, you can still participate in this research study. Do you request that we send important medical findings from your study tests/exams to your personal physician?

[ ] Yes [ ] No _____ Initials

Identifiers (your name, address, date of birth, etc.) will be removed from the private information or biospecimens that are collected as part of this research. When the identifying information is removed your private information or biospecimen may be used for future research studies or given to other research investigators without getting additional informed consent from you or your legally authorized representative.

As part of this research study, you will be asked to provide a blood sample for genetic testing. DNA, or deoxyribonucleic acid, is material in our bodies that contains genes. It stores and transmits inherited traits, such as eye color or blood type. As part of this study, your DNA will be studied in an effort to find out if there are genes that influence medical conditions that are part of this study. Specifically, we would like to know if identified risk genes for dementia may alter how people respond to movement or social engagement. We will not examine your DNA to diagnose health conditions, or to do clinical genetic testing or genetic counseling. Because we do not know how the results of this DNA study relate to your individual health, the results of the research will not be given to you or your doctor, or be placed in your medical records. Your blood that will be collected for genetic testing, even if identifiers are removed, will not be used or distributed for future research.

Storage of Biological Tissue

If you agree to participate in this study, we will draw about 1/2 a tablespoon of blood from your arm to use for future research. This sample will be kept and may be used in future research to learn more about other diseases. Your sample will be obtained in the Geriatrics Research Center at Wake Forest University Baptist Medical Center. The sample will be stored in the Claude D Pepper Center Repository at Wake Forest Baptist Medical Center under the direction of Dr. Barbara Nicklas, and it will be given only to researchers approved by Christina Hugenschmidt, PhD, the PI of this study. An Institutional Review Board (IRB) must also approve any future research study using your tissue sample. In order to participate in this study, you must be willing to provide this sample for future research.

Your blood sample will be stored with a unique identifier and will not include any identifiable information about you such as your name, address, telephone number, social security number, medical record number or any of the identifiers outlined in the HIPAA Privacy Rule. The unique identifier will be a randomly assigned number and only the principal investigator will have access to the code that links the unique identifier to you. Your name, address, social security number, etc., will never be disclosed to future researchers and neither will the code that links your identifiers to the sample.

How Long Will I Be in the Study?

You will be in the study for around 3 to 4 months. This includes pre-testing, the 8 week intervention, and a final follow-up phone call. You can stop participating at any time. If you decide to stop participating in the study, we encourage you to talk to the investigators or study staff first to learn about any potential health or safety consequences. Even if you stop participating in the intervention, we may contact you to see if you are willing to complete follow-up testing unless you specifically request that we do not.

What Are the Risks of the Study?

Being in this study involves some risk to you. You should discuss the risk of being in this study with the study staff. Risks and side effects related to the study procedures we are studying include:

- Blood sampling. You may experience discomfort, bruising and/or bleeding where the needle is inserted. Occasionally, some people become dizzy, lightheaded or feel faint. Infection may occur on rare occasions. Frequent donation of blood can result in low iron in your blood (iron deficient anemia).

- Cognitive tests. You will be asked to complete some short tests of thinking and memory. The tests may be given orally, written on paper, or on a computer. These tests may be recorded for scoring purposes. The testing in these visits is not intended or adequate for diagnostic purposes. Careful instructions will be given before the testing. There is a risk that some people may feel frustrated or worried when taking the tests. Please talk with study staff and let them know if you experience distress.

- Administration of estrogen. Estrogen administration has known risks in postmenopausal women. Side effects associated with short–term estrogen replacement therapy may include nausea, breast tenderness, spotting or bleeding that is sometimes similar to menstrual bleeding (monthly period), and mild skin irritation at the patch site. Heavy postmenopausal bleeding is not expected and would warrant an MD evaluation. The dose of estrogen used in this study (50-100 pg/ml) is commonly used in clinical practice with a very low incidence of adverse effects. If you have a uterus, progestin will be prescribed at the end of the study to reverse potential endometrial stimulation. In addition, your estrogen levels will be monitored during the second week of estrogen administration to ensure they are between 50-100 pg/ml. A study coordinator will contact you weekly to monitor safety and ensure compliance.

- MRI Scan. The MRI machine does not use radiation (such as x-rays) and is considered safe. You will be asked to wear earplugs, which we provide, since operation of the machine can produce noises that may cause discomfort. With earplugs, the risk to hearing is insignificant. Some people may experience discomfort in the scanner if they are uncomfortable in tight places, known as claustrophobia. No serious biological effects have been reported from MRI scans. You can stop the MRI test at any time. Trained medical personnel are always in attendance during these tests.

- PET Scan. PET scans use radiation, or nuclear medicine imaging, to produce 3-dimensional images. This radiation dose is not expected to produce any harmful effects. Some people may experience discomfort in the scanner if they are uncomfortable in tight places, known as claustrophobia. A needle will be used to inject [11C] acetoacetate and [18F] fluorodeoxyglucose into a vein in your arm. Insertion of the needle may cause pain or a stinging sensation at the injection site. On rare occasions the insertion of a needle can cause bleeding, a blood clot, swelling or infection at the site of insertion. You may also experience a burning or stinging sensation when the compound is injected.

If you participate in this study, you will be exposed to amounts of radiation above what you would normally receive in daily life. To be sure that you do not receive an unhealthy amount of radiation from your participation in this study, you should let your study doctor know if you have had, or are going to have, any other scans or x-rays as part of your medical or dental care. It is very important that you let your study doctor know if you already are participating in, or plan to participate in, any other research study that involves radiation exposure. This research study involves exposure to radiation from the PET scan. The amount of radiation that you will receive from this is equivalent to a uniform whole-body dose of 2.61 rem. This is equal to 52% of the yearly radiation exposure limit allowed for a radiation worker (5 rem).

When the above scans are viewed for research purposes, occasionally an area that appears abnormal may be observed. This is called an “incidental finding”. It is called “incidental” because it happens when you are not having any health problems that might cause your doctor to request that test, but rather is seen incidentally when we are looking for something else. Incidental findings may alert you to a previously unknown health problem. However, the scans we perform are for research purposes, not diagnostic purposes. That means that incidental

findings may *not* reflect a real problem if a diagnostic scan is performed later. Because incidental findings can result in unnecessary testing, not everyone wishes to know if we observe one. Please let us know if you would like to be informed.

[ ] I wish to be informed if there is an incidental finding on my MRI or PET scan.

[ ] I do not wish to be informed if there is an incidental finding on my MRI or PET scan.

In addition, there is a slight risk of a breach of confidentiality. We will do our best to protect your confidential information. There also may be other side effects that we cannot predict. You should tell the research staff about all the medications, vitamins and supplements you take and any medical conditions you have. This may help avoid side effects, interactions and other risks.

Taking part in this research study may involve providing information that you consider confidential or private. Efforts, such as coding research records, keeping research records secure and allowing only authorized people to have access to research records, will be made to keep your information safe.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

You are not expected to receive any direct benefit from taking part in this research study. We hope the information learned from this study will benefit other people in the future.

WHAT OTHER CHOICES ARE THERE?

This is not a treatment study. Your alternative is to not participate in this study.

WHAT ARE THE COSTS?

All study costs, including any study medications and procedures related directly to the study, will be paid for by the study. Costs for your regular medical care, which are not related to this study, will be your own responsibility. You will receive parking vouchers that will cover the cost of parking for your study visits

WILL YOUR RESEARCH RECORDS BE CONFIDENTIAL?

The results of this research study may be presented at scientific or medical meetings or published in scientific journals. Your identity and/or your personal health information will not be disclosed unless it is authorized by you, required by law, or necessary to protect the safety of yourself or others. There is always some risk that even de-identified information might be re-identified.

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or

local civil, criminal, administrative, legislative, or other proceedings, see below); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects.

The Certificate cannot be used to refuse a request for information from personnel of the United States federal or state government agency sponsoring the project that is needed for auditing or program evaluation by the National Institute on Aging (NIA) which is funding this project or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). You should understand that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it.

The Certificate of Confidentiality will not be used to prevent disclosure as required by federal, state, or local law. The Certificate of Confidentiality will not be used to prevent disclosure for any purpose you have consented to in this informed consent document.

WILL YOU BE PAID FOR PARTICIPATING?

You will be paid $350 if you complete all the scheduled study visits. If you withdraw for any reason from the study before completion you will be paid $25 for the screening visit, $50 for each complete cognitive and MRI visit, $25 for completing the check of estrogen levels, and $100 for each PET imaging study visit. To receive payment, you must provide your social security number, name and address so that we can comply with IRS (Internal Revenue Service) reporting requirements. When payments are reported to the IRS we do not let them know what the payment is for, only that you have been paid. If you do not wish to provide this information you can still take part in this study but you will not be paid.

WHO IS SPONSORING THIS STUDY?

This study is being sponsored by The National Institute on Aging (NIA), one of the National Institutes of Health. The sponsor is providing money or other support to Wake Forest University Health Sciences to help conduct this study. The researchers do not, however, hold a direct financial interest in the sponsor or the product being studied.

WHAT HAPPENS IF YOU EXPERIENCE AN INJURY OR ILLNESS AS A RESULT OF PARTICIPATING IN THIS STUDY?

Should you experience a physical injury or illness as a direct result of your participation in this study, Wake Forest University School of Medicine maintains limited research insurance coverage for the usual and customary medical fees for reasonable and necessary treatment of such injuries or illnesses. To the extent research insurance coverage is available under this policy the reasonable costs of these necessary medical services will be paid, up to a maximum of $25,000. Wake Forest University Baptist Medical Center holds the insurance policy for this coverage. It provides a maximum of $25,000 coverage for each claim and is limited to a total of $250,000 for all claims in any one year. The Wake Forest University School of Medicine, and the North Carolina Baptist Hospitals, Incorporated do not assume responsibility to pay for these

medical services or to provide any other compensation for such injury or illness. Additional information may be obtained from the Medical Center's Director of Risk and Insurance Management, at [redacted].

If you are injured, the insurer may require information such as your name, social security number, and date of birth in order to pay for your care. This is because the insurer is required by law to report any payments made to cover the care of any persons who are members of a government insurance plan to the Department of Health and Human Services.

You do not give up any legal rights as a research participant by signing this consent form. For more information on medical treatment for research related injuries or to report a study related illness, adverse event, or injury you should call Christina Hugenschmidt, PhD at [redacted] during normal business hours and at [redacted] after hours and ask for the geriatrician on call.

WHAT ABOUT MY HEALTH INFORMATION?

In this research study, any new information we collect from you and/or information we get from your medical records or other facilities about your health or behaviors is considered Protected Health Information. The information we will collect for this research study includes: information about your current medications and health diagnoses; brain images; testing of memory and cognition.

We will make every effort to keep your Protected Health Information private. We will store records of your Protected Health Information in a cabinet in a locked office or on a password protected computer.

Your personal health information and information that identifies you ("your health information") may be given to others during and after the study. This is for reasons such as to carry out the study, to determine the results of the study, to make sure the study is being done correctly, to provide required reports and to get approval for new products.

Some of the people, agencies and businesses that may receive and use your health information are the research sponsor; representatives of the sponsor assisting with the research; investigators at other sites who are assisting with the research; central laboratories, reading centers or analysis centers; the Institutional Review Board; representatives of Wake Forest University Health Sciences and North Carolina Baptist Hospital; representatives from government agencies such as the Food and Drug Administration (FDA) or the Office of Human Research Protections (OHRP), the Department of Health and Human Services (DHHS) and similar agencies in other countries. Some of these people, agencies and businesses may further disclose your health information. If disclosed by them, your health information may no longer be covered by federal or state privacy regulations.

Your health information may be disclosed if required by law. Your health information may be used to create information that does not directly identify you. This information may be used by other researchers. You will not be directly identified in any publication or presentation that may

result from this study unless there are photographs or recorded media which are identifiable.

Monitors, auditors, IRB or other regulatory agencies will be granted direct access to the participant's original medical record for verification of clinical trial procedures or data, without violating confidentiality of the participant and to the extent permitted by other applicable laws.

If required by law or court order, we might also have to share your Protected Health Information with a judge, law enforcement officer, government agencies, or others. If your Protected Health Information is shared with any of these groups it may no longer be protected by federal or state privacy rules.

Any Protected Health Information collected from you in this study that is maintained in the research records will be kept for at least six years after the study is finished.

You can tell Dr. Christina Hugenschmidt that you want to take away your permission to use and share your Protected Health Information at any time by sending a letter to this address:

Christina Hugenschmidt, PhD
[redacted]

However, if you take away permission to use your Protected Health Information you will not be able to be in the study any longer. We will stop collecting any more information about you, but any information we have already collected can still be used for the purposes of the research study.

By signing this form you give us permission to use your Protected Health Information for this study.

If you choose to participate in this study, your medical record at Wake Forest University Baptist Medical Center will indicate that you are enrolled in a research study. Information about the research and any medications or devices you are being given as a participant may also be included in your medical record. This part of the medical record will only be available to people who have authorized access to your medical record. If you are not a patient at this Medical Center, a medical record will be created for you anyway to ensure that this important information is available to doctors in case of an emergency. Information about your participation in the study will be placed in the NCBH medical record, along with any routine medical test results that were obtained at NCBH as part of this study.

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

Laboratory test results and other medical reports created as a result of your participation in the

research study may be entered into the computer systems of Wake Forest University Health Sciences and North Carolina Baptist Hospital. These will be kept secure, with access to this information limited to individuals with proper authority, but who may not be directly involved with this research study.

WHAT ARE MY RIGHTS AS A RESEARCH STUDY PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or you may leave the study at any time. Refusing to participate or leaving the study will not result in any penalty or loss of benefits to which you are entitled. If you decide to stop participating in the study we encourage you to talk to the investigators or study staff first to learn about any potential health or safety consequences. The investigators also have the right to stop your participation in the study at any time. This could be because it is in your best medical interest, you had an unexpected reaction, you failed to follow instructions, or because the entire study has been stopped

You will be given any new information we become aware of that would affect your willingness to continue to participate in the study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or in the event of a research-related injury, contact the study investigator, Christina Hugenschmidt, PhD at [redacted] during normal business hours and at [redacted] after hours and ask for the geriatrician on call.

The Institutional Review Board (IRB) is a group of people who review the research to protect your rights. If you have a question about your rights as a research participant, or you would like to discuss problems or concerns, have questions or want to offer input, or you want to obtain additional information, you should contact the Chairman of the IRB at [redacted] or the Research Subject Advocate at [redacted].

You will be given a copy of this signed consent form.

SIGNATURES

I agree to take part in this study. I authorize the use and disclosure of my health information as described in this consent and authorization form. If I have not already received a copy of the Privacy Notice, I may request one or one will be made available to me. I have had a chance to ask questions about being in this study and have those questions answered. By signing this consent and authorization form, I am not releasing or agreeing to release the investigator, the sponsor, the institution or its agents from liability for negligence.

Subject Name (Printed):_____

Subject Signature: _____ Date: _____Time:_____ am pm

Person Obtaining Consent (Printed):_____

Person Obtaining Consent:_____ Date:_____ Time:_____ am pm