EFFECTS OF EARLY USE OF DUAL THERAPY OF DAPAGLIFLOZIN WITH METFORMIN ON GLYCEMIC VARIABILITY IN MEXICAN PATIENTS WITH TYPE 2 DIABETES MELLITUS. AN OPEN-LABEL RANDOMIZED CLINICAL TRIAL.

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INFORMED CONSENT LETTER TO PARTICIPATE IN THE PROJECT:

EFFECTS OF EARLY USE OF DUAL THERAPY OF DAPAGLIFLOZIN WITH METFORMIN ON GLYCEMIC VARIABILITY IN MEXICAN PATIENTS WITH TYPE 2 DIABETES MELLITUS. AN OPEN-LABEL RANDOMIZED CLINICAL TRIAL.

You have been invited to participate in a clinical research study. Your participation in this study is strictly voluntary, meaning you may or may not choose to be part of it. This form describes the risks and potential benefits of the protocol so that you can decide whether or not you wish to participate and make an informed decision. This consent form describes the project: Effects Of Early Use Of Dual Therapy Of Dapagliflozin With Metformin On Glycemic Variability In Mexican Patients With Type 2 Diabetes Mellitus. An Open-Label Randomized Clinical Trial.

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INTRODUCTION:

This informed consent aims to explain the procedures, potential benefits, and risks of this protocol. This form explains how your medical information will be used and who can see it. You can obtain a copy of this form to review it at your leisure or to seek advice from someone else.

The study doctor or study staff will answer any questions you may have about this form or the study. Please read this document carefully and do not hesitate to ask about this information. This form may contain words you do not understand. Please ask the study doctor or study staff to explain any words or information that are not clear to you.

Once you read the informed consent form, if you wish to participate, you will be asked to sign the pages of this document. You will be given a signed original copy of your consent form to take home and keep for your records.

At the end of the explanation, you should understand the following points:

I. The procedures that will be used and their purpose, including the identification of which procedures are experimental.
II. The expected risks or discomforts.
III. The justification and objectives of the research.
IV. The benefits that may be observed.
V. Alternative procedures that might be advantageous for you.
VI. Assurance of receiving answers to questions and clarifying any doubts about the procedures, risks, benefits, and other matters related to the research and the subject's treatment.
VII. Your freedom to withdraw your consent at any time and stop participating in the study, without affecting your care and treatment at the Institute.
VIII. The assurance that you will not be individually identified and that the confidentiality of information related to your privacy will be maintained.
IX. The investigator's commitment to provide you with updated information that may be obtained during the study, even if this could affect your willingness to continue your participation.
X. The availability of medical treatment and compensation to which you are legally entitled, in case of damages caused directly by the research.
You may request more time or take this form home before making a final decision in the coming days.

INVITATION TO PARTICIPATE AS A RESEARCH SUBJECT AND PROJECT DESCRIPTION

Dear Mr./Ms.

The National Institute of Medical Sciences and Nutrition Salvador Zubirán (INCMNSZ), through the research group, invites you to participate as a research subject in this study, which aims to:

Evaluate whether there is a difference in glucose level control at different times of the day by comparing two types of treatment: One using two medications (metformin and dapagliflozin) and another using only metformin.

The total duration of the study is 13 weeks.

Your participation in the study will last 13 weeks.

The approximate number of participants will be 88 adults, recruited exclusively at the INCMNSZ, in Mexico City.

You were invited to the study because you have a diagnosis of type 2 diabetes of no more than 6 months, in your recent routine tests it was detected that the average of your blood sugar levels over the last 3 months is elevated (i.e., outside the desired goals) and you are also overweight or

obese.

For adequate control of your diabetes, in addition to following an appropriate diet and exercise plan, you need to take medication to lower your blood sugar levels. Particularly in this study, Metformin will be used, a medication that acts on the liver, intestine, and muscle so that your body produces and absorbs less sugar in your blood and responds better to insulin (a hormone that helps your body use sugar better), and Dapagliflozin, which is a medication that allows excess sugar in your blood to be eliminated through urine.

Currently, it has been observed that it is not enough to lower blood sugar levels for adequate diabetes control and prevention of complications, but it is equally important to prevent these sugar levels from changing abruptly throughout the day, i.e., to remain within an adequate range constantly, without sudden rises and falls. This protocol aims to evaluate whether the use of two medications (metformin and dapagliflozin) is better for maintaining stable glucose levels than the use of a single medication (metformin). You have the same probability of belonging to the group that only takes Metformin or the group that uses both medications at the same time (i.e., a 50-50 chance). This depends on the result of a random selection and not on the investigators.

STUDY PROCEDURES

The study lasts 13 weeks, with a total of 6 visits within the protocol and 2 visits outside the protocol. In the first two weeks (Visit 1 OP and 2 OP), you will be asked to take Metformin, and the dose will be adjusted to what your body tolerates best. If you do not tolerate it, you will not be able to continue in the study. On Visit 1 OP, a tilt table test will be performed at the National Institute of Cardiology Ignacio Chavez. After these two weeks, a random selection will be made for the group you will belong to, and monitoring that measures blood sugar variations will be placed for one week. After that, for 12 weeks (Visits 2 P, 3 P, 4 P, 5 P, and 6 P), different blood tests and medical evaluations will be performed, in addition to continuing treatment with the corresponding medications.

Each visit will last 2 hours. For some visits, the investigator may go to your home or a video consultation may be conducted.

On Visit 1 OP and 6 P, the following study will be performed:

- Tilt Table Test:

This study requires fasting for approximately 10 to 12 hours. You will lie on your back, electrodes and a cuff will be placed to monitor heart rate and blood pressure, a sling and a glove will also be placed to measure pulse, an IV with saline solution will be inserted, a device will be placed on your skull to measure blood flow to your brain, you will remain lying on your back for 5 minutes and standing for 30 minutes, after which the test will be completed, lasting approximately 45 minutes.

On Visit 1 OP, the following study will be performed:

- Physical Activity Questionnaire:

A questionnaire about your daily activities will be completed, with which we will measure the energy you spend doing physical activity in a day and it helps us monitor insufficient physical activity as one of the main risk factors for non-communicable diseases.

- Food Record:

You will be provided with a form in which you will record the food consumed daily throughout the protocol to assess adherence to the diet.

On Visit 1 P and Visit 5 P, the following study will be performed:

- Blood Sugar Variation Monitoring:

In this study, a device called iPro™2, approximately 5 centimeters in size, will be placed on your abdomen. It has a sensor that records your glucose levels at different times of the day. You will wear it for 7 continuous days, after which it will be removed and the obtained records will be analyzed. This study may cause slight discomfort when placed on the skin and may cause irritation in the area, but it is temporary and does not pose a health risk. Since it will be used for 7 days at the beginning of the protocol and one week at the end, you will wear the device for a total of 14 days.

On Visits 1 P, 2 P, 3 P, 4 P, 5 P, and 6 P, the following studies will be performed:

- Blood and Urine Samples:

The amount of blood taken at each visit is equivalent to a quarter cup of water (50 mL) and will be analyzed for fat levels (total cholesterol, HDL, LDL, triglycerides), liver function (ALT, AST), kidney function (creatinine, creatinine clearance, uric acid, albuminuria, vesicle measurement), and blood glucose. These tests will allow for a better evaluation of the treatments' effect on your body.

Additionally, the effectiveness of the medications in controlling your glucose levels will be determined by performing two tests that measure the amount of sugar in your blood (glycated hemoglobin and fructosamine) and the hormone that regulates sugar (insulin). Two other tests will also be performed to evaluate if the elevation of glucose in your blood is causing damage to your arteries or veins: One test measures the degree of oxidants (substances that damage cells, accelerating their aging and death), and the other measures substances that indicate inflammation.

In total, blood and urine tests will be taken on 4 occasions. You should come for sample collection after an 8-hour fast.

- Glucometry Record:

You will be asked to measure your glucose daily and record it on a form that will be provided at each visit. This is a minimally invasive procedure, involving a finger prick to extract a drop of blood

and calculate daily blood glucose.

- WHO Physical Activity Questionnaire
- Food Record
- Body Fat Quantification:

A special test will be performed to quantify or measure the amount of fat in your body.

Your responsibility as a participant in the study is:

- Attend visits when indicated.
- Allow blood samples to be taken.
- Take the medications indicated for your treatment.
- Notify the investigators of any discomfort you experience during the study (called a drug adverse effect).
- Do not take any type of herbal product or supplement.
- Do not take any medication not prescribed by the study doctors or inform them of any other product or medication you need to take.

RISKS AND INCONVENIENCES

Because this is a research study where medications are being administered, it is considered a Grade III risk study (meaning the risk is greater than the minimum possible) even though the medications being evaluated have been approved for several years and their efficacy and safety have been proven, as there is a possibility that the medications may not work properly or may cause you certain discomforts.

The risks of blood sample collection are: possibility of slight bleeding or bruising at the puncture site, dizziness or feeling faint, and rarely the blood vessel from which the sample is taken may be injured. The personnel who will draw the blood sample are trained to do so, which will reduce the risks of complications. Extra blood samples may be taken during the study if the study doctor deems it necessary to monitor your health/safety. It may be necessary to obtain a blood sample more than once.

There is no risk of any kind in obtaining a urine sample.

You may also experience discomfort during the placement of the continuous glucose monitoring equipment, such as pain at the catheter insertion site and the possibility of slight bleeding at the catheter puncture site.

No risk or discomfort is expected during body fat measurement.
No risk is expected during the tilt table test.

BENEFITS

By deciding to participate in this research study, your overall health will be evaluated more frequently compared to standard treatments currently available, which gives you an advantage as a patient in better managing your disease.

The additional tests that will be performed will allow for better control of your sugar levels and also evaluate how other organs in your body, such as the liver, kidneys, and blood vessels, are functioning.

The medications administered during the study will lower your sugar levels and are expected to help you reach ideal control goals to prevent or reduce the damage that diabetes can cause.

ADVERSE EFFECTS OR REACTIONS OF THE MEDICATIONS YOU WILL TAKE DURING THE STUDY:

Like all medicines, dapagliflozin can cause side effects, although not everybody gets them. Stop taking dapagliflozin and see a doctor immediately if you notice any of these serious side effects:

- **Excessive fluid loss from the body (dehydration):** Occurs infrequently (may affect up to 1 in 100 people). Signs of dehydration: Very dry or sticky mouth, feeling intensely thirsty, feeling intensely drowsy or tired, little or no urine during the day, rapid heartbeat.
- **Urinary tract infection:** Occurs frequently (may affect up to 1 in 10 people). Signs of a urinary tract infection: Fever and/or chills, burning sensation when urinating, back or side pain. Although not very common, if you notice blood in your urine, tell your doctor immediately.
- **Fournier's gangrene:** 12 cases have been reported over a 5-year period. It is a serious infection of the skin of the genitals or the area between the genitals and the anus. Signs of Fournier's gangrene: Pain, tenderness, redness, or swelling of the genitals or anus, fever, or a general feeling of being unwell. These symptoms can worsen quickly, so it is important to tell your doctor immediately so that treatment can be given as soon as possible. If its presence is suspected, broad-spectrum antibiotics and surgical debridement will be administered immediately if necessary.
- **Excessive decrease in blood sugar levels (Hypoglycemia):** Occurs frequently when combined with other glucose-lowering medications. Signs of excessive decrease in blood sugar levels: Chills, sweating, feeling very anxious, rapid heartbeat, feeling hungry, headache, vision changes, mood changes, or feeling confused. Your doctor will explain how to treat low blood sugar levels and what to do if you experience any of the above signs.
- **Diabetic ketoacidosis:** It is rare in patients with type 2 diabetes (may affect up to 1 in 1,000 people). Signs of diabetic ketoacidosis: frequent nausea or vomiting, stomach pain, excessive thirst, rapid and deep breathing, confusion, unusual drowsiness and tiredness, a sweet smell on your breath, a sweet or metallic taste in your mouth, a different smell in your urine or sweat, and rapid weight loss. This can occur regardless of blood sugar levels. Your doctor should decide whether to temporarily or permanently discontinue your dapagliflozin treatment.

REPORTING ADVERSE EFFECTS

If you experience any side effect, talk to your doctor or nurse, even if it is a possible side effect not listed in this document.

The administration of metformin also presents side effects, and gastrointestinal discomfort such as nausea, vomiting, diarrhea, abdominal pain, and loss of appetite is very common. However, these discomforts resolve spontaneously in most cases. Taste disturbances may also occur. People treated with metformin for a long time may experience reduced vitamin B12 absorption, leading to low blood levels and an increased risk of anemia.

The most serious complication, although very rare, is lactic acidosis. It occurs mainly in people with severe damage. It should be suspected in the presence of symptoms such as difficulty breathing, abdominal pain, muscle cramps, fatigue or tiredness, decreased body temperature, which can ultimately lead to a coma. If acidosis is suspected, metformin should be stopped and immediate medical attention sought.

CONCOMITANT MEDICATIONS

Any medication you take, other than the research study medication, including herbal remedies and other non-traditional remedies, is considered a concomitant medication. The study doctors will review with you the concomitant medications you can continue taking and those you cannot take during your participation in the study.

CONFIDENTIALITY ASPECTS OF YOUR MEDICAL INFORMATION

Your name will not be used in any public reports of the study. The laboratory samples obtained will not contain any personal information and will be coded with a serial number to avoid any possibility of identification. By legal provision, laboratory samples, including blood, are classified as hazardous biological-infectious waste, and for this reason, your sample cannot be returned to you during the course of the research. Your laboratory samples, as well as your medical and/or genetic information, may be used for other research projects related to the disease under study. They cannot be used for research studies related to conditions other than those studied in this project, and these studies must be submitted for approval by an Ethics Committee.

Your samples may be stored by the investigators until the necessary samples are obtained for subsequent analysis.

The codes that identify your sample will only be available to the principal investigators, who are legally obligated not to disclose your identity. These codes will be stored in a locked filing cabinet. Only the investigators will have access to them. Study personnel (monitors or auditors) may have access to participant information.

There is a possibility that your privacy may be affected as a result of your participation in the study, if necessary to protect your rights and well-being (for example, if you have suffered an injury and require emergency treatment) or if requested by the relevant authority.

Your confidentiality will be protected as required by law, by assigning codes to your information. The code is an identification number that does not include personal data. No information about you will be shared with others without your authorization.

If you decide to withdraw from the study, you may request the withdrawal and destruction of your

biological material and information. All data collection forms will be kept with the same confidentiality measures, and only the principal investigators will have access to the data that includes your name. If you wish to do so, you should contact Dr. Miguel Ángel Gómez Sámano and express your decision in writing.

The INCMNSZ Research Ethics Committee approved the conduct of this study. This committee reviews, approves, and supervises research studies in humans at the Institute. In the future, if we identify information that we consider important for your health, we will consult with the Research Ethics Committee to decide the best way to provide this information to you and your doctor. Furthermore, we request your authorization to contact you, if necessary, to request information that could be relevant to the development of this project.

The scientific data obtained as part of this study may be used in publications or medical presentations. Your name and other personal information will be removed before using the data.

If you request it, your primary care physician will be informed about your participation in the study.

COMPENSATION

There are no costs to you if you participate in this study, and there will be no charges for office visits, tests, or procedures associated with the study. You will not receive monetary compensation for your participation. Your transportation costs to attend your visits cannot be covered by the institute. In the event of adverse reactions to any of the study medications, these will be attended to and will not generate additional costs for you. In case of hospitalization due to a serious event related to the study medications, there is a medical insurance policy.

PARTICIPATION AND WITHDRAWAL FROM THE STUDY:

Remember that your participation is VOLUNTARY. If you decide not to participate, neither your usual relationship with the INCMNSZ nor your right to receive medical care or any service will be affected. If you decide to participate, you are free to withdraw your consent and discontinue your participation at any time without prejudice to your care at the INCMNSZ. You will be informed in a timely manner if new information is obtained that may affect your decision to continue in the study.

The study may be terminated prematurely if you experience:

- Allergy due to dapagliflozin
- Severe life-threatening illness
- Pregnancy during the study
- Acute kidney damage
- Inability to tolerate at least 1000 mg/day of metformin.

In case you are required to withdraw from the study prematurely, the accepted and recommended standard treatment for your condition will be offered.

BIOETHICAL APPROVAL

Both this informed consent form and the research protocol were reviewed and approved / received a favorable opinion from the Research Ethics Committees and the Institute's Research Committee, to safeguard the rights, safety, and well-being of all patients participating in this research study.

IDENTIFICATION OF INVESTIGATORS:

In case you suffer harm related to the study, please contact Dr. Miguel Ángel Gómez Sámano at INCMNSZ (phone: 5527614851).

If you have questions about the study, you can contact Dr. Miguel Ángel Gómez Sámano at INCMNSZ (phone: 5527614851).

If you have questions about your rights as a study participant, you can speak with the president of the INCMNSZ Research Ethics Committee (Arturo Galindo Fraga, phone: 54870900 ext. 6101).

ACTIONS TO FOLLOW AFTER THE STUDY ENDS:

You can request the results of your clinical tests and the study conclusions from Dr. Miguel Ángel Gómez Sámano at INCMNSZ (tel. 5527614851). Research is a long and complex process. Obtaining the final results of the project may take several months.

INFORMED CONSENT STATEMENT

I have carefully read this informed consent, have asked all the questions I had, and all have been answered satisfactorily. To participate in the study, I agree with all the following points:

I agree to participate in the study described above. The general and specific objectives of recruitment, and the possible harms and inconveniences have been explained to my full satisfaction.

I agree to voluntarily donate my biological samples (blood and urine samples) to be used in this study. Likewise, my medical and biological information may be used for the same purposes.

I agree, if necessary, to be contacted in the future if the project requires collecting additional information or if they find information relevant to my health.

My signature also indicates that I have received a duplicate of this informed consent form.