CLINICAL TRIAL PROTOCOL

Predicting Glycemic Events (Hypo or Hyperglycemia) utilizing a non-invasive monitoring device

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1. SUMMARY

Adequate glycemic control in patients with Diabetes Mellitus (DM) is a desired therapeutic goal that is difficult to achieve with current blood glucose monitoring technology. An important limiting factor in achieving glycemic control is the risk of hypoglycemia. The importance of avoiding hypoglycemia is both because it can cause important adverse events like seizures, unconsciousness, and even death, and because a hypoglycemic state often led to over-correction with food and hyperglycemia.

Home Blood Glucose Monitoring (HBGM) technology, which requires finger pricking, is a source of severe inconvenience to the patients and hence, a lack of compliance. The common practice is to measure blood glucose less frequently than desired; this severely hinders the ability to safely control blood glucose levels. Continuous glucose monitoring (CGM), although easier for patients, is an invasive device that some patients find inconvenient. Additionally, these devices cannot predict an impending event. Such a prediction of impending an event for example would allow the patient the opportunity to potentially avoid a hypoglycemic event by eating. Thus, the need for non-invasive and easy to operate glucose monitoring in DM patients for strict glycemic control cannot be overemphasized.

The goal of this feasibility study is to test whether the Tedence Ltd non-invasive device, based on the measurement and analysis of Extremely Low Frequency- Electromagnetic Field signals, can be used to predict an impending glycemic event and specifically, will be able to recognize the tendency to hypoglycemic/hyperglycemic episodes 15-60 minutes before the actual hypoglycemic/hyperglycemic event. This will be done by performing hypo and hyperglycemic clamp in patients with Type 1 diabetes (T1D) and comparing the results of the glucose levels readings from any commercially available CGM system to signals obtained from the non-invasive ELF-EMF Tedence sensing device. For the control group, we will use non diabetic subjects that will wear the ELF-EMF Tedence device.

2. BACKGROUND

Improved glycemic control can minimize many of the complications associated with diabetes[i]. However, tight glycemic control in patients using insulin and other drugs that can cause hypoglycemia increases the risk of a hypoglycemic episode. Frequent self-monitoring of blood glucose (BG), often using a CGM system, combined with intensive insulin therapy, using either multi-daily insulin injection (MDII) or insulin pump, greatly improves glycemic control in patients with T1D. Most recently, the use of automatic hybrid closed loop (AHCL) further improves glucose control in patients with T1D, however, none of these systems can predict an impending abnormal event. Currently, glucose is monitored by measuring capillary blood from the fingertips, from venous/arterial line blood samples and from a CGM or flash technology. However, the prediction of hypoglycemic/hyperglycemic episodes before their occurrence is not always accurate and early enough in all of these devices. Continuous accessible non-invasive sensing at an affordable price is one of the means to address this issue of attempting euglycemia in patients with diabetes, specifically in patients with T1D, as the frequency of hypoglycemic events/glucose variability in this population is higher than amongst patients with Type 2 Diabetes (T2D). A reliable non-invasive glycemic event monitor is the first step towards improved diabetes management.

3. OBJECTIVES

The primary objectives of the trial are to determine:

3.1 The ability of the Tedence Ltd non-invasive Extremely Low Frequency-Electromagnetic Field (ELF-EMF) sensing device to identify a hypoglycemic event defined as glucose <, = 60 mg/dl

3.2 The ability of the Tedence Ltd non-invasive ELF-EMF sensing device to identify a hyperglycemic event defined as glucose >, = 200 mg/dl equal or greater

3.3 The safety of the non-invasive Tedence Ltd non-invasive ELF-EMF sensing device in predicting abnormal glycemic events.

4. STUDY ENDPOINTS

4.1 Accuracy Endpoints:

To assess the ability to predict impending glycemic events as evaluated by:

- Comparison with values measured by a hospital laboratory device.
- Mean relative error when compared to venous blood glucose measured by a laboratory device and by any CGM device that can provide a CGM output that can be used for ELF-EMF measurement correlation analysis.
- Clarke Error Grid with measurements of venous blood as the comparing value

4.2 Hypoglycemia recognition:

- The ability of the Tedence Ltd device to accurately recognize a near-hypoglycemic event of glucose of up to 70 mg/dl,

4.3 Safety:

Safety will be evaluated in a descriptive manner by recording all adverse events in the patient population by number and severity.

The study will evaluate safety by assessing:

a. Device-related adverse events: local and systemic effects of the Tedence Ltd non-invasive ELF-EMF sensing including: redness, burns, pain, or other complications
b. General adverse events: Adverse events not directly related to the non-invasive Tedence Ltd non-invasive ELF-EMF sensing device but are related to the study procedure (i.e., clamping), such as: local infection, blood clot, bleeding and hypoglycemia

5. STUDY DESIGN

The study is a feasibility, prospective, study that is designed to test the capabilities and safety of the Tedence Ltd non-invasive ELF-EMF sensing during a hypo and hyper

glycemic clamp in 10 patients with Type 1 diabetes. The control group will comprise 10 individuals who are normoglycemic and not pre-diabetic. The subjects will be connected to the device for 3-6 hours.,

Each patient must meet the eligibility criteria and provide signed informed consent prior to entering the study.

For the control group: normo-glycemic, non-pre-diabetic subjects, will be recruited using the diabetes clinical research unit data-base and advertisement in Hadassah Medical Center. Upon arrival, participants vital signs will be measured (e.g., pulse and blood pressure) and afterwards will be connected to Tedence Ltd non-invasive ELF-EMF sensing. They will be observed for a 3 hour period and released.

For the clamp intervention group: Glucose clamp technique is a method for quantifying insulin secretion and resistance. It is used to measure either how well an individual metabolizes glucose or how sensitive an individual is to insulin. In our patients the hyperinsulinemic clamp (injection of insulin to induce hypoglycemia) will be followed by correction of hypoglycemia via ingestion of Inshure drink. Each day consists of approximately 3-6 hours, during which, near-hypoglycaemic and hyper clamp will be done. Following completion of the trial, the ELF-EMF signals obtained from the Tedence Ltd non-invasive ELF-EMF sensing device will be compared to the readings obtained from both the venous, the laboratory blood measurements and from the output of the commercially available CGM system (such as FreeStyle Libre 2) .

During each of the clamp's days:

1. The subject will arrive after a night's fast (8 hours).
2. The subject will be set up in a clinic. A physician and a research assistant will be present at the clinic during the entire experiment and will check the patient at each stage.
3. At the beginning of the experiment the subject will be examined for vital signs (body temperature, pulse rate, respiration rate, and blood pressure).
4. 2 IV lines will be placed to be used for both, infusion of Insulin and Glucose, and for drawing blood samples.

5. The subject's initial BGL will be 80-140 held stable for 20 minutes and afterwards decreased using IV Insulin infusion (1-2 cc at a time of 100 IU Human Insulin in 100 cc NaCl 0.9%) until the lowest BGL limit of 70 mg/dl will be reached, or until the patient will feel any signs of hypoglycemia- weakness, shaking or any other inconvenient feelings.
6. The subject's blood glucose levels will be constantly measured with the patients' CGM system. Concomitantly thenon-invasive Tedence Ltd ELF-EMF sensing devices will record the patients' ELF-EMF signals. ,
7. Hyperglycemia will be induced by the subject's consumption of Ensure Plus suspension (up to 2 cans).
8. After the highest- 250 mg/dl limit blood glucose level (BGL) will be decreased in steps of 50mg/dl or of 100mg/dl (from 200mg/dl) up to the limit of 150 mg/dl using IV Insulin infusion.
9. After the last measurement at the end of the 20 minutes stable on 150 mg/dl, the experiment will be over, and the patient will eat and inject SC short acting insulin according to the investigator direction.
10. After the last experimental stage, the patient will remain at the clinic for observation until the glucose level stabilizes at 100-200 mg/dl.
11. The subject will be examined again for vital signs.
12. The patient will be checked by a physician for any adverse reaction. The subject will be discharged home when he feels well, his blood glucose levels are stabilized at 100-200 mg/dl and the physician will approve it.
13. A follow-up phone call visit will be done the following day in order to assess any adverse events after the intervention.

6. ELIGIBILITY

6.1 Study population

The study will recruit two different population of patients:

1) For the healthy control population, we will recruit:

   Patients without diabetes/ pre-diabetes or any other serious illness that in the investigator opinion can risk the patient.

   Ages: 18 to 65.

   Signed informed consent.

   Not involved in active military duty

Females-non-childbearing potential or females of childbearing potential who have a negative pregnancy test (HCG in blood or urine) within 72 hours of informed consent.

2) The patient population will include subjects with relatively controlled type 1 diabetes mellitus.

6.2 Inclusion criteria

- Type 1 Diabetic patient with a Hgb A1C <=9.0 .
- Actively utilizing a CGM system such as the Freestyle Libre 2 or Medtronic Guardian 3 or 4 etc
- Ages: 18 to 65.
- Signed informed consent.
- Not involved in active military duty.
- Females-non-child bearing potential or females of child-bearing potential who have a negative pregnancy test (HCG in blood or urine) within 72 hours of informed consent and during the second visit before the clamping procedure.

6.3 Exclusion criteria – for both groups

- Active systemic or local infection.
- Any medical condition that, by the investigator judgment, will increase the risk from Hyper and Hypo-Glycemic clamp: seizures, heart disease, hypoglycemia unawareness etc.

- History of malignancy, radiotherapy, or chemotherapy for malignancy (except BCC of the skin)

7. TREATMENT PLAN

7.1 Assessment of Eligibility and enrollment

Subjects will be enrolled from the Diabetic Unit of Hadassah Medical Center and must meet the inclusion criteria indicated above.

7.2 Informed consent

The patient's consent to participate in this study must be given in writing. Each patient will receive a full explanation of the procedure and will hold a copy of the signed informed consent. Admission of the patient into the study will be recorded in the medical records.

7.4 Clinic Visits and Events -

Visit 1-Screening and baseline visit

Baseline visit will take place in the diabetic Unit, and the following data will be collected:

- Informed consent
- Full name (and assigned initials)
- Date of birth
- Medical history and medications
- Physical examination
- Complete blood count
- Serum chemistry
- Pregnancy test

Visit 2 –Day one of the study: up to four weeks following Visit 1

1. The subject will arrive after a night's fast (8 hours).
2. Vital signs will be measured before the clamp.
3. Hypo and Hyper -Glycemic clamp will be done, as described above, during which, the Tedence Ltd non-invasive ELF-EMF sensing device will be placed on the patient.
4. Document adverse events
5. Document concomitant medications.
6. Vital signs will be measured after the clamp.
7. Subjects will be contacted the following for adverse events assessment.

7.6 Special Methods

7.6.1 Standard Laboratory measurements

The standard laboratory measurements performed in this study include hematology, serum chemistry, and urine or serum pregnancy tests (for women of child-bearing potential). The specimens for these tests will be collected at the study site, according to standard hospital and laboratory procedures. All specimens will be analyzed at the study site laboratory facility. The laboratory reference ranges and current laboratory certification will be obtained from the hospital laboratory facility.

7.7 Patient Withdrawal

The physician may withdraw a patient from the study at any time. Patients that are withdrawn from the study after treatment intervention will continue the follow-up as scheduled to obtain safety intervention.

8. TRIAL MATERIALS AND PROCEDURE

8.1 Tedence Ltd non-invasive ELF-EMF sensing Device

It has been reported in the literature, pulses of ELF-EMF might reduce blood sugar levels in animal models of metabolically induced Diabetes. The mechanism of action for this phenomenon is believed to be via improved efficiencies within the Redox pathways of cellular mitochondria. Tedence Ltd hypothesizes that hypo or hypoglycemic events may induce changes in the EMF of mitochondria and that such changes may be picked up by the ultra-sensitive Nivio and Migne sensors and that such changes may predict impending glycemic events.

The Tedence Ltd non-invasive ELF-EMF sensing device is based on Nivia xMR and Migne sensors graciously provided by TDK Corporation (Tokyo, Japan). These sensors can detect magnetic fields with high sensitivity, approaching pico tesla level, which is under 1/1,000,000 of the geomagnetic field. AC magnetic field (0.1Hz-2KHz) in the dynamic range of +/- 60uT can be accurately measured. achieved to be up to ±250 nT. The magnetic noise density shows 3 pT/√Hz at 1 Hz in the recommend circuit, and it enables to use various usages as super low noise magnetic field sensor.

We will be applying three sets of sensors with each set consisting of Nivio and Migne sensors to each patient/subject. One set will be placed on the skull, another over RUQ of the abdomen (liver region) and another set on the forearm. No skin preparations are needed. All sensors are attached to a CPU via wires. The device does not create any heat or other sensation and is inert to the patient/subject. A fourth and final set of sensors will be placed in the room to measure background signals and will not be applied to the subject.

The output of these sensors will be analyzed utilizing AI algorithms and correlated to various glycemic events that occur throughout the clinical experiment.

8.2 Laboratory blood measurements

Laboratory blood measurements are used for detailed analysis of different products in the blood. These measurements will include levels of blood glucose.

8.3 Commercially available CGM Systems

Commercially available CGM systems such as Abbott Freestyle Libre 2 Medtronic Guardian 3 or 4, and any other such CGM system that can export the graph or actual glucose measurements to a computer device are acceptable .

9. STATISTICAL ANALYSIS

9.1 Sample Size

For this exploratory pilot study we would like to perform a clamp study on up to 10 Type 1 DM patients and up to 10 non-diabetic/pre-diabetic control subjects

9.2 Primary Endpoint-Safety

Safety will be assessed by the number and severity of adverse events.

9.3 Accuracy Analysis

Upon completion of the trial, the sponsor will be supplied with the following:

A. All non-invasive Tedence ELF-EMF readings
B. The glucose levels as measured by any commercially available CGM system throughout the duration of the trial period
C. The venous glucose levels as measured by the laboratory hexokinase glucose determination for the trial period
D. The laboratory blood measurements made in the hospital laboratory

9.3.1 Correlation Analysis

To relate ELF-EMF signals to adverse events and, furthermore, use them to predict those, several steps on the hardware and software levels are to be performed. There are many

technical aspects, related to an accurate measurement of low-intensity magnetic fields. The main challenge comes from numerous environmental noises, which severely affect the measurement, given the fact that the signal under investigation has a rather small intensity. Noise sources will be separated into external (i.e., electronic equipment, moving metallic objects in a surrounding, etc.) and internal (i.e., related to a patient's motion). To minimize the impact of external sources, differential detection with a pair of calibrated detectors is performed. Furthermore, partial shielding is obtained with permalloy (or any other material). Internal noises will be correlated with motion detectors, connected to patients. The data from accelerometers will be correlated with EMF measurements to factor out a motion.

After collecting signals, a neural network (or any other learning algorithm) will be applied to collate EMF signals with the ground truth (the data from medical equipment, e.g., glucometer). The main objective of the entire protocol is to find a reliable correlation.

10. ADVERSE EVENTS

Adverse events comprise all disturbances of general health, subjective and objective signs of disease (including laboratory abnormalities), inter current disease, and accidents observed in the context of a clinical trial, irrespective of a possible causal relationship with the use of a trial device.

10.1 Adverse reactions

Adverse reactions are adverse events caused wholly or partly by the intervention. A casual relationship between an observed adverse event and the use of the trial intervention may exist with various degrees of probability, on the basis of statistical probability, or of plausible medical data and considerations. Unless such a

relationship is established, adverse events observed in a clinical trial should not be designated adverse side effects.

10.2 Serious adverse events

Serious adverse events are those that are life-threatening or are suspected of being life-threatening or cause severe and lasting damage to the patient's health. This is particularly true for events that could be fatal, are life-threatening, can cause malignant disease or congenital deformities, cause permanent damage or require admission to hospital during the major part of medical treatment.

10.3 Anticipated Adverse Events

10.3.1 Hypoglycemia

The definition of hypoglycemia according to the American Diabetes Association:

- Mild hypoglycemia: Glucose < 70 mg/dl (3.9 mmol/L), symptoms of hypoglycemia controlled alone without the assistance of others.
- Severe hypoglycemia: The need of assistant from other person to treat the hypoglycemia.
- In a case of hypoglycemia, the patient will receive food. During the entire clamp the patient is connected to 5% glucose and if necessary will be treated with IV Glucose.

10.3.2 Bleeding: As complication of vein puncture, will be handled by applying local pressure.

10.3.3 Infection: As rare complication of vein puncture, will be handled by applying local or systemic antibiotic**.**

10.3.4 Blood clot: As rare complication of vein puncture, will be handled as required.

10.4 Recording and documentation

Every adverse event is recorded in the Case Report Form. The following data must be documented:

- Type of event
- Patient number
- Time of occurrence: date, time
- Duration: hours, days
- Severity degree: mild / moderate / severe

Level	Course	Intensity	Outcome	Causality
1 =	isolated event	mild	complete recovery	unlikely
2 =	recurrent	moderate	improved	possible
3 =	continuously	severe	unchanged	probable
4 =		unknown	worsened	established
5 =			death	not established
6 =			unknown	a = expected
				b = unexpected

10.4 Causality

Relation to the study device:

– Unlikely: there is sufficient information showing that there is no relationship between etiology and study treatment.

– Possible: close temporal relationship. Adverse event was previously described as adverse event of the treatment or can be expected. It could also be attributable to numerous other causes.

– Probable: close temporal relationship. Adverse event has already been described in regard to the treatment or can be expected. Improvement or disappearance of

adverse event after ceasing treatment. Probable adverse events which cannot be attributed to the clinical condition of the patient.

– Established: close temporal relationship with the use of the study treatment. An already known or expected symptom in connection with the treatment. Improvement or disappearance of the symptoms after ceasing treatment. Reappearance of symptoms on re-exposure.

– Not assessable: Assessment of the relationship to the study treatment is not possible.

11. ORGANIZATION

Clinical center

The study will take place in the Diabetes Unit, Hadassah Ein Kerem hospital.

Data collection and confidentiality

Case Report Forms (CRF) will be maintained for each patient participating in the study. Erroneous values and/or text must not be obliterated. Instead, the error must be crossed out in a single line, the correct value/text added and the correction initialized and dated by the investigator. All materials will be kept for a period of at least 15 years and available for auditing or inspection by the health authorities. All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential.

Ethics

The study will be conducted in accordance with the guidelines of the Declaration of Helsinki. All participating investigators declare that they are informed of the standards of conduct of clinical trials as laid down in the EN-540 (Clinical investigation of medical devices for human subjects) and the Declaration of Helsinki. Documented approval from the Ethics Committee will be obtained prior to study start, according to ICH GCP, local

laws, regulations and organization. When necessary, an extension, amendment or renewal of the Ethics Committee approval will be obtained.

Study administration

The administration of the study will take place at the Diabetes Unit, Hadassah Hospital, Ein Kerem.

12. REFERENCES

[i] The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The New England Journal of Medicine Vol. 329, No. 14, Sep 1993: 977–86.

Sensors

TDK Nivio Sensor

TDK Migne Sensor