Title: Comparison of Meal-Time Dosing of Rapid Acting Insulin Using Carbohydrate Counting vs. Fixed Doses Utilizing Continuous Glucose Monitoring In Patients with Cystic Fibrosis Related Diabetes

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Background and Introduction

Cystic fibrosis related diabetes (CFRD) is the most common extra-pulmonary comorbidity in patients with cystic fibrosis (CF). CFRD is also associated with accelerated decline in pulmonary function, increased pulmonary exacerbations and increased mortality. Continuous glucose monitoring (CGM) involves the use of a small disposable sensor sited in the subcutaneous interstitial fluid that makes frequent glucose measurements. There is data suggesting that the Medtronic iPro continuous glucose monitors (CGM) can predict hemoglobin a1c levels in patients with CFRD.

The aim of our study is to assess the utility of CGMs to determine the optimal method to dose meal-time insulin. We will examine glucose excursions in patients with CF who will dose meal-time rapid acting insulin by carbohydrate counting versus fixed dose rapid acting insulin. The carbohydrate ratio and fixed doses will be determined by existing doses, total daily insulin doses, body weight and insulin sensitivity along with predisposition to hypoglycemia. Bolus insulin dosing is an important part of CFRD management due to the high nutritional demands on these patients. If dosed incorrectly, this could lead to marked hyperglycemia and could worsen nutritional status due to urinary glucose losses. In this project, we will perform a within subjects' comparison of the 2 standard methods of meal-time rapid acting insulin dosing.

Hypothesis:

1. We hypothesize that postprandial interstitial fluid glucose levels in patients who utilize carbohydrate counting to dose mealtime rapid acting insulin will have improved control as defined as area under the curve and time in target compared to patients who used fixed dose mealtime insulin
2. Our second hypothesis is that patients who utilize carbohydrate counting will have fewer hypoglycemia events compared to patients who use fixed dose meal-time insulin

Specific Aims:

1. To compare within-subject glucose excursions defined as percentage of time in target glucose level, percentage of glucose in target and peak post prandial glucose with fixed insulin dosing versus carbohydrate count based insulin dosing.
2. To compare the frequency and duration of hypoglycemia (defined as daily, weekly and average duration of event) between insulin delivery methods described above.
3. To test the use of 'rule of 500' for carb counting estimation in CFRD patients.
4. To compare the effect of two methods of rapid acting insulin delivery on fasting glycemia

Research Design and Methods

Subject population:

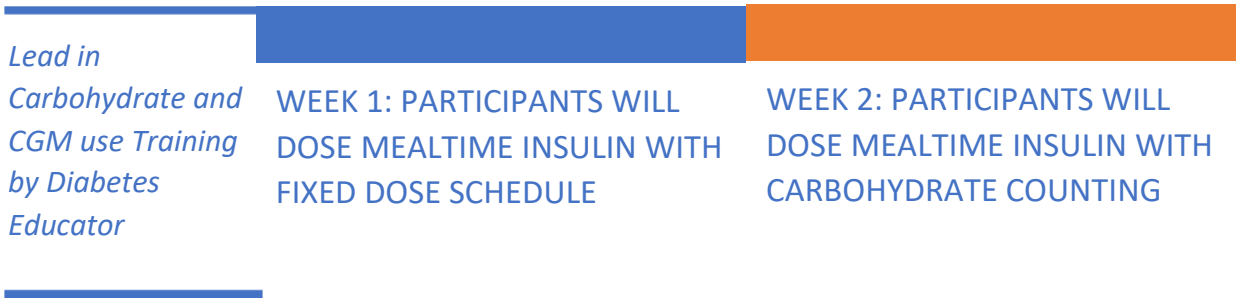
Adult patients with a diagnosis of CFRD will be recruited from the CF Center at the University of Pittsburgh. Sample size will be 20 patients. Inclusion criteria will be adults >18 age of years with diagnosis of CFRD (as defined by standard 2-hour oral glucose tolerance test (OGTT) Patients who are being evaluated for transplant and patients who already use CGM will be excluded. Stable lung transplant patients who are more than 1 year from transplantation will be included. The patients will be individually followed in the adult CF Endocrine clinic. Downloads and data gathering will be performed at the clinic during follow up visits.

Methods

CGM involves the use of a small sensor sited in the subcutaneous interstitial fluid that makes frequent glucose measurements. The Wake Forest School of Medicine Endocrinology Division (WFBSM) will provide us with Abbott Freestyle Libre CGM patches to use in our CF patients. All patients will be recruited from the UPMC adult CF Center and the CF Endocrine Clinic. The CGMs will be placed in our clinic on patients recruited from the Cystic Fibrosis center. Downloads and data gathering will be performed at our center. The project will be performed in collaboration with partners from WFBSM. There will be study design input from collaborators at WFBSM as well as statistical support if needed.

Each sensor is valid for a 2-week period of use and these sensors automatically stop gathering data beyond 14 days. Each participant will be provided carbohydrate counting education and training prior to their participation by certified diabetes educators at UPMC. During the first seven days of wear, the participants will be asked to dose their meal time rapid acting insulin by fixed dose and the next 7 days, participants will be asked to dose their meal time rapid acting insulin by carbohydrate counting. Patients will be required to maintain a paper log of their carbohydrates consumed at every meal and snacks and insulin doses given during the 2-week time frame. The CGM will record blood sugars once every minute in a blinded fashion and participants will not be aware of the CGM recording data. At the completion of the 14-day period, participants will return their CMG devices for analysis and interpretation. If they live at a distance from our office and are unable to visit us to return the device, they will be permitted to mail in the sensor along with the food and glucose logs. The data will be summarized and

communicated to the patients once analyzed. Patient will be required maintain fingerstick blood sugar logs. The figure below describes the various study periods:



Measurement:

Thorough literature search found only one other study examining inpatient carbohydrate counting. Three other studies were identified that examined other insulin regimens inpatient and their effect on hypoglycemia and hyperglycemia rates. The statistical analysis methods of those studies were used as a benchmark for this study

Data Points:

Primary: We will be measuring postprandial excursions on continuous glucose monitoring data and the instances of hypoglycemia during the two-week timeframe of the study period

Secondary: Total carbohydrates consumed each day during the two-week time frame, total daily dose of insulin per 24 hour period (midnight to midnight) will be secondary endpoints

CGM devices can be connected to desktop machines and downloaded via a receiver. The baseline characteristics that will be collected are age, sex, race, exocrine pancreatic function status, CFTR genotype, duration of CFRD, hemoglobin A1c, renal function tests, weight and BMI. From the log, insulin doses and fingerstick glucoses will be collected. The outcome measures that will be extracted from the CGM devices to assess the effectiveness of our intervention in improving glycemic control and nutritional status will include daily glucose trends calculated by percentage of time in target interstitial fluid glucose levels level and percentage of target interstitial fluid glucose levels readings, hypoglycemia episodes, and average glucose from the 2 comparison periods. This data will be compared for statistical significance using student t-test with significance assigned to p-value less than 0.05.

The clinical endocrine fellow will collect data from each included patient by performing a Cerner and Epic (EHR) chart review. Data will be recorded on an encrypted UPMC OneDrive Microsoft excel spreadsheet with password restricted access. A list of collected data points are as follows:

1. Age
2. Sex

3. Race
4. Exocrine pancreatic function status (sufficient vs. insufficient)
5. CFTR genotypes
6. Duration of CFRD
7. Weight and BMI at the most recent office visit or on the day of the placement
8. Labs: serum creatinine and eGFR (most recent value in the last 12 months), hemoglobin a1c (the most recent value in the last 3 months, or will be performed by point of care testing at the time of the CGM device placement)
9. Modulator use: ivacaftor (Kalydeco), lumacaftor/ivacaftor (Orkambi), tezacaftor/ivacaftor (Symdeko), elexacaftor/tezacaftor/ivacaftor (Trikafta); start date and duration of use
10. Meal /snack time insulin doses from log
11. CGM glycemic control data (percentage of time within glycemic target)
12. Data from fingerstick before and after intervention
13. Nutritional information with carbohydrates consumed per meal/snack in grams

Study power: This is a proof-of-concept study and we plan to include 20 patients in this study which we expect will be adequately powered to demonstrate a trend and compared intrasubject variation between the 2 study periods.

Controls/patient demographics: Patient demographics are shown in table 1, while variables to be measured are shown in table 2.

Data safety:

Data for individual patients will be deidentified without names, addresses, DOB, or SSN. Individual patients will be classified as patient 001, 002, 003 etc.

A subject identifier key will be used to match the medical record number with a subject ID number. The subject identifier key will be maintained in a password protected Excel file. Collected information on the data collection tool will be entered into a separate password protected Excel file. One year after the conclusion of the study, all collected data will be destroyed by permanently deleting electronic copies. The principal investigator and study team members will not disclose PHI to any other person or entity.

All individuals involved in the completion of this study will take every precaution to ensure the safety and confidentiality of all patient information. This will include the use of an encrypted UPMC OneDrive Microsoft excel spreadsheet with restricted access. No patient information will ever be stored on personal devices or on an external hard drive/flash drive.

Statistical Analysis:

We will perform a within subjects statistical comparison using student t-test to compare CGM glucose values, time in target glucose level, percent of glucose values in target and hypoglycemia events during each week using the 2 standard methods of meal-time rapid acting insulin dosing. The data will be analyzed by SPSS statistical software package.