Continuous glucose monitoring for post-kidney transplantation in pre-existing type 2 diabetes

Study Protocol

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1. BACKGROUND AND SIGNIFICANCE

About 20,000 kidney transplants take place yearly in the US. Diabetes (DM) is the most common cause for end-stage kidney disease (ESKD) [1] and the most common clinical condition listed for kidney transplant (31%) [2]. Glucose levels are relatively controlled during ESKD (due to prolonged insulin action, reduced glycogen stores, decreased renal gluconeogenesis). Glycemic control is then disrupted in the early post-transplant period because these processes are reversed with the transplanted kidney, patients develop insulin resistance from high dose glucocorticoids and other anti-rejection medications, and their appetites increase [3].

Cleveland Clinic performs around 250 kidney transplants a year, and has successfully reduced the patients' length of hospital stay (LOS) post-transplant from 5 days down to 3 days by developing an enhanced recovery after surgery (ERAS) pathway that has a large outpatient diabetes management component. That is, patients no longer stay in the hospital to have their multiple daily insulin injection (MDII) doses adjusted. This necessitates having a reliable source of glucose readings when they are discharged to adjust their MDII doses and avoid hyperglycemia/hypoglycemia, and potentially reduce readmissions, rejection, and delayed graft function. Continuous glucose monitoring (CGM) is a method of measuring patients' glucose readings every 5-10 minutes via subcutaneous insertion of a sensor, reducing or even eliminating the need for painful fingerpricks (fingerpricks can be done as needed if there is discrepancy between the CGM reading and the patients' clinical scenario).

2. SPECIFIC OBJECTIVES:

1) Primary objectiveobjective

To characterize the glucometrics (description of glucose readings in relation to target goals, as discussed in the Methods section), achieved by a CGM-based insulin titrating protocol for glucocorticoid taper for post kidney transplant patients

2) Secondary objective:

To explore the relationship between CGM glucometrics and rates of readmission, rejection, and delayed graft function in post kidney transplant patients

3. RESEARCH DESIGN AND METHODS

3.1Primary endpoints

1) Ambulatory glucose profile (AGP) data glucometrics such as time in range, time below range, time above range, and glucose variability (coefficient of variation)
2) Readmission
3) Rejection
4) Delayed graft function

3.2 Secondary endpoints

1) Levels of HbA1c at 3 months and 6 months post-transplant
2) Diabetes medication adjustment at each time point (SEE schedule of assessments)

If YES, which of the following occurred (can be more than one answer)	• reduction of any insulin dose • stopped the scheduled insulin • stopped the correction insulin • stopped the basal insulin • started a non-insulin medication
If NO, which of the following occurred (can be more than one answer)	• stayed on the same insulin doses • increased one or more insulin doses • started a non-insulin medication without decreasing the dose of insulin

Categorical and continuous variables that will be collected closest to time of signed consent (last available recorded value for continuous variables):

1) Age

2) Sex

3) Weight

4) Height

5) BMI

6) HbA1c and serum glucose reading

7) Glucometrics based on CGM AGP, and individual CGM glucose reading download (Freestyle Libre readings are averaged every 5 minutes)

8) Serum creatinine

9) eGFR

10) Original kidney disease

11) Length of hospital stay for kidney transplant admission

12) Readmission (including reason)

13) Delay of graft function (defined as needing dialysis in the first 7 days post-transplant)

14) Rejection

15) Diabetes mediation and dose

16) Appetite (qualitative: poor, fair, good, great)

17) Carbohydrate intake (dietary recall): grams of carbohydrate per meal

18) Prednisone taper schedule (standard upon inclusion but will note if changed to rapid)

19) Tacrolimus, other anti-rejection medication dose

20) Transferred to what type of provider (PCP/local endocrinologist/CCF endocrinologist) after 3 months

21) CGM upload (Enrollment –visit 10) with Abbott Libre. CGM upload (after visit 10) if patient has other CGM prescribed- percent of CGM time above range, in range, below range (TAR, TIR, TBR), or very high, high, in range, low, very low

22) Freestyle Libre or other CGM use pre and post-transplant

a) If not on CGM: what are the patients' reasons for not being on a CGM, or for not using consistently (e.g. insurance issues, durable medical equipment company delay, does not want to continue, no mobile app, provider not refilling/not incorporating into management)

b) If utilizing Freestyle Libre CGM, allow us to look at retrospective data OR patient to upload AGP from the previous visit. If patient on a different CGM, patient to upload AGP from previous visit.

3.3 Recruitment

A total of 20 patients that are post kidney transplant, will undergo intervention until 3 months post-transplant. Informed consent will be obtained prior to start of study. The final visit will be at 3 months. Patients will be discharged to their local endocrinologist or primary care physician at this 3-month mark. Data will continue to be gathered for 3 more months after exit from intervention.

Enrollment will be within the first 2 weeks of hospital discharge.

Screening of patients will be done through the inpatient endocrinology consult list (seen in various floors in the main campus hospital), or the endocrine kidney transplant clinic list (patients seen at Q8). Endocrine providers (physicians, nurse practitioners, pharmacists) who take care of qualifying patients will inform patients of this study at their visits again only mentioning a research study involving CGMs and kidney transplant patients. The endocrine providers will notify the study staff if the patient has questions or would like to learn more. The study staff will follow-up with the patients, provide and thoroughly review the consent. The patients will be given time to review the consent ask questions prior to making a decision to participate. The consenting process will take place in a private exam room if outpatient, or in the hospital room if still admitted to the hospital. The process will be documented in EPIC.

Visits are standard of care (SOC) at the Kidney Transplant Clinic or at the Endocrinology clinic and will be virtual or in-person or telephone encounter (see table). Visits are twice a week for the first 3 weeks post discharge. Following this, visits will be every two weeks until the end of the steroid taper(final steroid dose), usually 7.5mg daily by 56 days after transplant (see table below). This is part of SOC.

Standard prednisone taper	
Post op day	Prednisone dose
2	60 mg twice a day
3	50 mg twice a day
4	40 mg twice a day

5	30 mg twice a day
6	30 mg AM and 15 mg PM
7-13	30 mg in AM
14-27	20 mg in AM
28-41	15 mg in AM
42-55	10 mg in AM
56 and beyond	7.5 mg in AM

At Enrollment, insertion of Freestyle Libre 2 (or later version) sensor will be placed on upper arm. An account will also be set up on Libreview.com. This is part of SOC with diabetic patients who use CGMs. The patient will be asked to sign up on the product's platform (in this case for Freestyle Libre Abbott products, Libreview.com). We will be collecting data from the CGM ambulatory glucose profile (AGP) report or from phone/reader if we are unable to link to the patient's portal for certain visits. An insulin dosing protocol would be set up per patient. The patients would have already been seen by the inpatient endocrine team during the admission for their kidney transplant and would have been discharged on multiple daily insulin injection (MDII). This is part of the early recovery after surgery (ERAS) pathway that we have developed with the kidney transplant team. When patient is outpatient, we address dosing in order of priority by reducing or increasing the corresponding insulin by 10-100%. The range is wide to account for some doses that might be small (e.g. 2 units of rapid-acting insulin, for prednisone dose reduction, and for a change in appetite). We also make allowance for changing to non-insulin medications, as shown in the table.

Acceptable percentage of time that glucose levels are at a certain range, and insulin adjustment		
Glucose e and percentage of time it is acceptable for glucose levels to be in these ranges		Insulin adjustment by 10-100% (the range is wide to account for some doses that might be small, such as 2 units of rapid-acting insulin, for prednisone dose reduction, and for a change in appetite
Time in very high range (>250mg/dL)	5% or less	Increasing the corresponding insulin if above 5%

Time in high (181-250 mg/dL) plus very high range	25% or less	Increasing the corresponding insulin if above 25%
Time In Range		
In range (70-180 mg/dL)	70% or greater	Continue to monitor but decrease if prednisone dose is decreasing
Time Below Range		
Time in low range (54-69 mg/dL) plus very low range	4% or less	Reducing the corresponding insulin if above 4% with option to reduce even if 4% or less (because we want to avoid further hypoglycemia)
Time in very low range (<54 mg/dL)	1% or less	Reducing the corresponding insulin if above 1% with option to reduce even if 1% or less (because we want to avoid further hypoglycemia)
Other insulin protocols		
Serum creatinine or eGFR is still elevated		Dose adjustments will be towards giving less insulin
Attempt to stop mealtime insulin and substitute with medication below		
Prednisone dose is 10mg daily or less	CGM shows >70% time in range	There is no contraindication to the medication to be started
Keep or reduce basal insulin. Keep the correction scale insulin while initiating medication changes below. Order with which medication switch is to be made; proceed to the next one on the list if there is contraindication or plan restriction.		

1. GLP-1 agonist
2. DPP-4 inhibitor
3. Sulfonylurea
4. Unable to use the other DM medication types yet at this early phase post-transplant

Stop correction scale insulin. As allowed by CGM pattern, increase basal insulin if needed to eliminate correction scale insulin.

Next attempt is to stop the basal insulin by increasing the dose of the GLP-1 agonist or DPP-4 inhibitor or sulfonylurea, or addition of a sulfonylurea to the GLP-1 agonist or DPP-4 inhibitor.

Outline of procedures

Events	Enrollment	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12
Time points	within 2 weeks of hospital dis-charge	1 week post discharge +/-3 days*		2 weeks post discharge +/-3 days*		3 weeks post discharge +/-3 days*		Week 5 +/-3 days*	Week 7 +/-3 days*	Week 9 +/-3 days*	Week 12 (3 mo) +/- 1 month	Week 18 (4.5 months)	Week 24 (6 mo) +/- 1 month
	In-person	In-person or virtual						Telephone encounter (unless patient wants an in-person or virtual visit)			In-person preferred, virtual if needed	Telephone encounter (unless patient wants an	Telephone encounter (unless patient

												in-person visit)	wants an in-person visit)
Consent	X												
Libreview Account Set-up, CGM insertion, CGM teaching	X												
CGM download	X	X	X	X	X	X	X	X	X	X	X	X[a2]	X[a2]
Demographics - age, sex, weight, height (height only on enrollment), BMI	X	X	X	X	X	X	X	X	X	X	X	X	X
Labs - serum crea/eGFR/serum glucose Optional for some visits, but these are SOC	X	X	X	X	X	X	X	X	X	X	X	X	X
HbA1c	X										X		X
Appetite evaluation (poor, fair, good, great)	X	X	X	X	X	X	X	X	X	X	X	X	X
Carbohydrate intake	X	X	X	X	X	X	X	X	X	X	X	X	X

(approximate grams, dietary recall)													
Diabetes medication review	X	X	X	X	X	X	X	X	X	X	X	X	X
Transplant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X
Ambulatory glucose profile (AGP) and individual glucose reading downloads		X	X	X	X	X	X	X	X	X	X	X[b]	X[b]
Document - Readmission/ rejection/ delayed graft function		X	X	X	X	X	X	X	X	X	X	X	X

Note: All visits and labs are Standard of Care (SOC). Serum crea/eGFR are ordered by the kidney transplant team. A1c is ordered by the endocrine team.

*Window variances measured in business days

a For those who remain on it; fingerstick for those who do not

b If still on CGM; survey if not on CGM

3.4 Statistical Methods

The goal of the present study is not hypothesis testing, but rather estimation. With 20 patients, and assuming that the standard deviation in the time in range will be no more than 20%, and time in range levels will be moderately correlated over time (r = 0.5), estimated changes in time in range will be estimated to within ±9.4%. Additionally, there will be at least 80% power to detect mean changes of at least 13.3% in time in range over time within patients. This sample size will allow us to generally estimate precision of the prevalence of binary events such as readmission and delay of graft function to within ±20% provided that the event rate is less than 30%.

Patient characteristics will be summarized overall and by group using means and standard deviations for continuous measures and frequencies and percentages for categorical factors. MedicationMedication adjustment as well as binary events such as readmission, rejection and delayed graft function rates will be estimated at each time point and compared over time using McNemar tests or generalized mixed effect models. Toevaluate continuous measures such as HbA1c and AGP metrics over time, paired t-tests or linear mixed models will be used. In these models, time will be the main predictor. Estimated HbA1c and glucometrics levels at each time with 95% confidence limits will be estimated from the model. Linear mixed models are valid under the assumption of missing at random. This will be evaluated graphically and, if necessary, sensitivity analyses will be performed to evaluate the potential effects of the missing data over time. If glucometric time measures are close to the extremes of the distribution (i.e. near 0 or 1), then an alternate approach using beta regression to estimate the levels and changes may be performed. Time to readmission and rejection will be estimated using Kaplan-Meier analysis. If interim analyses result in a change to the insulin dosing protocol, results will be presented overall, and then separately for the first 10 and last 10 patients. Stratification of results may also be performed based on the timing of enrollment relative to the transplant. Analysis will be performed using SAS software (version 9.4; Cary, NC) or R software (version 4.1; Vienna, Austria). Given that this is a pilot study, we will perform all tests using a 0.05 significance level, and focus on estimation to allow for future research, if warranted.

4. STUDY POPULATION

This is a non-randomized perspective single arm study with a planned enrollment of 20 patients.

4.1 Inclusion Criteria

1. Sex: men and women
2. Ethnicity: all ethnic groups
3. Age: ≥ 18
4. Known type 2 diabetes before kidney transplant
5. Kidney transplant alone
6. On multiple daily insulin injection
7. Standard prednisone taper
8. Smart phone – compatible with the LibreView App

4.2 Exclusion Criteria

1. Simultaneous pancreas-kidney transplant
2. Allergy to Freestyle Libre components including adhesive
3. Use of vitamin C at doses 500 mg or greater
4. Blood dyscrasias that prevent hemoglobin A1c interpretation
5. Lack of mobile app accessibility
6. Rapid prednisone taper

In the uncommon scenario, if a patient is started on a standard prednisone taper and converted to a rapid prednisone taper. The patient would remain in the study.

4.3 Adverse Events and Data Monitoring Committee (DMC)

There will not be a data monitoring committee for this pilot project. Any AE or SAE will be reported to the PI, Sponsor and IRB in a timely manner once they have been disclosed to study personnel.

Unanticipated non-serious adverse events assessed by the PI as being either caused by, or related to, the study procedures, will be reported using the Adverse Event Report form.

The following adverse events are anticipated as a result of the blood collection required per the study procedures: pain, bruising, bleeding or infection at the site where the blood was collected from the subject. Fainting may also occur as a result of blood collection. Because these events are anticipated, they do NOT need to be reported using the Adverse Event Report form as long as they are not assessed as serious. If assessed as serious, then they need to be reported.

There may be some risks from wearing the Continuous Glucose Monitor (CGM)

- Skin irritation at the insertion site which may include redness and rash
- Infection at the insertion site (redness, soreness, warm or hot skin, drainage noted)
- Discomfort
- The sensor may fall off accidentialy and need to be reinserted
- Exposing the sensor to MRI, CT scan, diathermy (electrically induced heat or the use of high frequency electromagnetic current as used in physical therapy or surgery), or x-ray may cause damage and incorrect readings. Patients will be asked to remove the sensor for these procedures.
- The sensor should not be submerged more than 3 feet (1 meter) or kept underwater longer than 30 minutes at a time.

Interim analysis of glucometrics:
Even though there is no DMC, we would like to see if our insulin dosing parameters are related to severe hyperglycemia and severe hypoglycemia. As such, we will do interim analysis after 10 patients. If among the first 10 patients, at least 4 patients report Time in Very High Range > 10% of the time, or Time in Very Low Range >5% of the time, then the insulin dosing protocol will be reviewed and modified.

5. DATA HANDLING AND RECORD KEEPING:

A file database will be created for data collection accessible only by authorized study personnel. Information will be entered into the database as it is collected and patients finish the study. Each patient will be assigned a study number consecutively as they are enrolled. Only the study number will be used to identify all study-related documents such as case report forms. A master list of study numbers linked to patient identifiers will be maintained by the study coordinator in a secured location. Study data will be collected and managed using REDCap (Research Electronic Data Capture); this will include patient identification number, medical record number, age, gender, and ethnicity.

If a subject withdraws from the trial or is lost to follow-up, then the subject's data which has already been collected will be retained by the investigator, entered into the database and used for the study reporting.

6. ETHICS:

The study will be conducted in compliance with ICH GCP and applicable regulatory requirements, and in accordance with the Declaration of Helsinki.

Voluntary signed informed consent will be obtained from each study subject prior to initiating any research interventions. Informed consent will be documented in the subject's medical record.

This study is subject to the review and approval of the Cleveland Clinic Institutional Review Board prior to initiating any study activities.

7. PUBLICATION PLAN:

Upon study completion, the data generated will be submitted in abstract form to an endocrine-, diabetes-, or kidney transplant-related meeting, and subsequently submitted to a journal for consideration for publication.

8. CITATIONS:

Burrows NR et al. Reported Cases of End-Stage Kidney Disease — United States, 2000–2019. MMWR Recomm Reports. 2022;71(11):412-415

Hart A et al. OPTN/SRTR 2019 Annual Data Report. Am J Transplant 2021;21(2):21-137

Iqbal A, Zhou K, Kashyap SR, Lansang MC. Early Post-Renal Transplant Hyperglycemia. J Clin Endocrinol Metab. 2022 Jan 18;107(2):549-562