“Improving Glycemic Control in DM2 Patients in the Ambulatory Setting”

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COVER PAGE

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Introduction

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Introduction

Managing patients with type 2 diabetes mellitus (T2DM) bears considerable challenges, as precise glucose monitoring and adherence to insulin therapy are necessary to guide therapeutic interventions. Although novel technological solutions such as automated insulin closed-loop delivery systems are available, many patients are treated with multiple daily insulin (MDI) regimens and use point-of-care (POC) fingerstick testing for glucose monitoring. POC testing is a relatively painful method with multiple limitations, including insufficient glucose information, lack of compliance, and potential errors (e.g., handwritten logs). In addition, obtaining accurate information on insulin administration is hindered by the prevalent use of traditional insulin pens. Consequently, when making treatment decisions, healthcare professionals (HPC) often rely on self-reported glucose values and the assumption that patients adhere to treatment plans. Unfortunately, insulin adherence among patients with T2DM is problematic, and many patients have poor compliance with insulin therapy.

Recent advancements in diabetes technology offer patients and HCPs efficient and reliable alternatives for obtaining glucose metrics and monitoring compliance. Continuous Glucose Monitoring (CGM) devices provide a sophisticated method of tracking glucose levels, gathering

high volumes of data continuously and automatically at frequent intervals. Additionally, Smart Insulin Pens (SIPs) record the timing and dosage of insulin, therefore documenting adherence. Utilizing software applications, data recorded by CGM and SIPs can then be shared with clinicians through Bluetooth and Internet connectivity.

Lifestyle intervention is also an essential component of diabetes treatment and managing patients with T2DM successfully involves promoting physical activity (PA). Increasing PA is associated with improved glycemic control, decreased risk of cardiovascular disease, and lower mortality. Despite its importance, most patients with T2DM remain physically inactive.

Optimizing glycemic control requires, however, frequent outpatient clinic visits for medication adjustments. Given that over 38 million Americans live with diabetes and approximately 90-95% of them have T2DM , managing such a high volume can be challenging through traditional face-to-face clinic visits. Additionally, many patients with T2DM have underlying comorbidities that restrict mobility or live in remote areas, posing barriers to seeking in-person care. Telemedicine can serve as an alternative method of providing less time-consuming and more accessible patient care, allowing quicker titration of DM medications and improving monitoring and compliance in medication taking. However, most patients continue to be seen through face-to-face visits, and previously described telemedicine systems are limited by POC testing and traditional insulin pens.

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With this study, we will perform a pilot randomized control trial (RCT) to examine the effectiveness and feasibility of a novel integrative telemedicine system for patients with T2DM, which combines CGMs, SIPs , official consultation from an exercise physiologist to promote PA and use of telecommunication methods.

Description of the Integrated Telemedicine Model

Our integrated telemedicine system is described below. First, to obtain glucose/insulin data, we will use a) CGM devices (Dexcom G6) and b) SIPs (Medtronic InPens for short-acting insulin and Insulclock Caps for long-acting insulin. Insulclock data will only be used for recording compliance and not for treatment decisions). Using Bluetooth technology and software applications, glucose, and insulin data from CGMs and SIPs will be sent to patients' smartphones, allowing them to make the recommended treatment decisions (e.g., prevent hypoglycemia, extra-correction insulin for hyperglycemia treatment, among others). Next, using program applications (i.e., Dexcom Clarity, Medtronic InPen), CGM/SIP reports will be generated to provide information relating to insulin nonadherence and patterns of hypo-hyperglycemia. Finally, HCPs will review the generated reports through commercial internet or Wi-Fi and use telecommunication systems (i.e., VA Video Connect (VVC), secure messaging (SM), or telephone call) to communicate with the patients and provide treatment recommendations. Additionally, during these telemedicine visits, an exercise physiologist (EP) will meet with participants remotely every three months. At the first EP appointment, a personalized and evidence-based PA prescription will be developed using information provided by the subjects to carry out the prescription (e.g., tips for making time to stay active and referral to technical instruction videos). In subsequent follow-up telemedicine visits, EP

provider will give personalized feedback on successes and challenges with performing PA and T2D behavioral skills.

Patient Population-Study Procedures

In this prospective, randomized control pilot study will be conducted at the Baltimore VA Medical Center (BVAMC), 30 patients with T2DM will be enrolled. Subjects who met at least one inclusion and none of the exclusion criteria defined below they will participate after they signed an informed consent.

Inclusion Criteria:

Insulin-treated patients with DM2 (treated with basal-bolus insulin regimens (MDI), ± non-insulin medications) and Uncontrolled glycemic control

Exclusion Criteria:

- History of type 1 DM (DM1)
- Pregnant Patients
- Extensive skin changes/disease or allergies that preclude wearing the CGM sensor
- Subjects who have end-stage renal disease requiring dialysis
- Significant psychiatric illness or any other condition rendering the subject incapable of understanding the objectives and potential consequences of the study

Participants will be randomly assigned using a computer-generated random sequence at a 1:1 ratio to either the Telemedicine group or the Standard of Care (SoC) group. All participants will be followed for six months, unless they died or if they withdrew consent and decided not to

continue participating in the study. No sample size calculations are provided due to the pilot nature of this study**.** Instead, we used a convenience sample of 30 subjects. This study was approved by the BVAMC IRB Committee.

Following consent, subjects in both groups will have a baseline research visit where they will be placed on a ("blinded") Dexcom G6 CGM device for ten days to obtain baseline CGM glucose data. A baseline assessment of PA will be obtained by completion of the Senior Fitness test. Subjects will be then randomized to either Telemedicine or the Standard of Care (SoC).

Participants in the telemedicine group will be educated about the appropriate use of the telemedicine system components. They will be asked to use their CGMs for ongoing automatic glucose monitoring, SIPs for insulin administration with recording insulin use, software applications, and VVC, SM, and telephone for telemedicine visits. Participants in the SoC will receive diabetes education as per standard of care (i.e., frequency of POC checking and proper insulin administration, among others). They will be asked to use POC for glucose monitoring and traditional insulin pens for insulin administration, and they will be asked to document POC, and insulin use as per standard of care.

Then, following the initial baseline visit, patients in the Telemedicine group will have the following interventions:

i) in-person (Initial) Clinic Visit (Day 0):

This will be a typical in-person clinic visit. Vital signs, medications, and a medical history will be obtained. POC values will be reviewed, and DM medication adjustments will be performed. CBC, BMP, HbA1c, and urine creatinine/microalbumin will be obtained per usual care.

ii) Telemedicine visits (~every three weeks until +180 days [end of RCT]):

Approximately every three weeks, patients will have remote visits using the DAT clinic. HCPs obtained CGM and SIP data using software applications (as above). Trends of hyperglycemia and hypoglycemia and their relationship with insulin administration will be identified, leading to adjustments of diabetes medications (insulin or non-insulin). Communication will be done by VVC, SM, or by phone. Patients will be evaluated more (i.e., if acute changes are needed after hypoglycemic events) or less frequently (i.e. if no changes on medications are needed). At the last remote visit (+180 days), all patients will have repeat lab work of CBC, BMP, HbA1c, and urine creatinine/ microalbumin.

iii) *Consultation (telecommunication) by an exercise physiologist (Days 0, +90 days, +180 days [end of RCT]):*

On day 0, the exercise physiologist will evaluate baseline PA data and medical history, telecommunicate with each participant regarding their PA goals, facilitators, and barriers, and will write a PA prescription (frequency/intensity/duration/type) following best practices 64. On days +90 and +180, he will discuss progress, set motivational intermediate goals to reach the long-term PA prescription objectives, and will modify exercises as needed.

iv) Research Visit: At +180 days (end of RCT):

Subjects will be placed on a "blinded" CGM. After ten days, Veterans will be asked to return the CGM, which will be downloaded. Subjects will complete the Senior Fitness test for PA evaluation.

Following the initial baseline visit, subjects in the SoC group will have the following interventions:

i) One in-person (Initial) Clinic Visit (Day 0):

This visit will be identical to the in-person visit that subjects will be randomized to the Telemedicine group had on Day 0.

ii) Two in-person Clinic Visits (Day +90, +180):

Subjects will have a typical clinic in-person visit. Vital signs and HbA1c will be obtained, physical examinations will be performed, and POC values (either by report, logbook, or glucometer) will be reviewed. Information regarding insulin use and adherence will be obtained through patient reporting. DM medication adjustments will be performed, and patients will be instructed to increase their PA as clinically indicated.

iii) One Research Visit: This visit will be at +180 days (end of RCT) and will be identical to the research visit of the Telemedicine clinic group.

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Outcome Measures

The purpose of this trial will be to examine the feasibility of the above interventions (CGMs, SIPs, Telecommunication systems and promoting PA by EP) combined as a single telemedicine intervention and examine whether it can lead to improvement in hyperglycemia, as defined by a decrease in HbA1c (primary outcome). Secondary outcomes will be time in range (TIR) 70-180 mg/dL, time below range (TBR) <70 mg/dL, TBR <54 mg/dl, time above range (TAR ≥180 mg/dL and TAR≥250 mg/dl. In addition, we will evaluate differences in hypoglycemic events (CGM glucose <70 mg/dL for at least 15 minutes), clinically significant hypoglycemic episodes (CGM glucose< 54mg/dL for at least 15 minutes), and nocturnal hypoglycemia. For glucose variability, we will evaluate if there is a difference in the Coefficient of Variation (CV).

STATISTICAL ANALYSIS

Student's t-test will be used to compare baseline characteristics of the two groups. For continuous outcome measures (e.g., HbA1c, time <54 mg/dl, etc.), we will use linear regression analyses (SAS proc genmod with a normal distribution and identity link). For outcome measures that will be counts (e.g., number of hypoglycemic episodes <54 mg/dl), we will use Poisson regression (SAS proc genmod with a Poisson distribution and a log link). Regardless of the type of regression we will use, the model will be change in outcome= baseline value + group + time + group + time where group will be control or telemedicine and time will be baseline, three-month, or six-month. We will calculate estimated values at each time point using the mean value of the outcome at baseline, baseline value, (SAS LSMeans statement with a pdiff option). Comparisons of baseline

characteristics will be performed using Student's t-test. A two-tailed $P \leq 0.05$ will indicate significance.