# RESEARCH PROTOCOL

**TITLE:** A Pilot Study on the Use of Real-Time Continuous Glucose Monitoring (RT-CGM) as a Tool for Weight Loss/Behavior Modification in Patients with Prediabetes and Diabetes

## RESEARCH PLAN

### A. Specific Aims

**Hypothesis:** We hypothesize that two sessions of 10 days of RT-CGM in the setting of nutrition and physical activity counseling coupled with education on how exercise and nutrition affect blood sugar levels will promote weight loss in participants with prediabetes and diabetes and reduce glycemic variability.

**Aim 1**: Examine the effect of two 10-day sessions of RT-CGM over 6 weeks on weight loss, change in body composition, activity level and nutritional changes in subjects with diabetes and prediabetes 12 weeks later.
**Aim 2:** Evaluate participants' perception of RT-CGM as a weight loss tool.
**Aim 3**: Evaluate the effect of RT-CGM on glycemic variability in subjects with prediabetes and diabetes.

### B. Background and Significance

In the United States, more than 29 million people have diabetes and 86 million adults have prediabetes (1). Annual medical costs for persons with diagnosed diabetes average $13,000, with approximately $7,900 being directly attributable to the disease (2). Many comprehensive lifestyle intervention programs such as the Diabetes Prevention Program (DPP) (3) and behavior change strategies (alone or in combination) have been used to promote weight loss in obese, high-risk individuals with variable effects. These include motivational interviewing, accountability/self-monitoring programs, food journals (4-6), pedometers (7, 8) and mobile phone apps (9) for weight loss.

There is widespread acknowledgment that lifestyle behavior change is critical for weight and glucose regulation. The National Institute of Diabetes and Digestive and Kidney Diseases' DPP trial (3) demonstrated that lifestyle changes (diet and physical activity aimed at weight loss) were more effective than metformin in preventing diabetes among those with prediabetes (6); however, the DPP lifestyle intervention involved frequent visits and coaching over several years, which is costly and labor intensive. More scalable adaptations for community translation, such as a 12-session group-based program called Group Lifestyle Balance™ (GLB) have been shown to be effective in community settings. A recent meta-analysis conducted in 2012 reviewing 28 DPP translational interventions had an average weight loss of 4%. However, the attrition rate or drop-out rate was as high as 50% in some programs and weight loss was highly dependent on number of core sessions attended (10). In a pilot project that we just completed in conjunction with the George Washington Milken Instituteof Public Health with younger African-American women, the drop-out rate was 35% and participation mean was 5.5 (range 2-11) for the 12 core sessions (11), highlighting the challenges of engaging patients in ongoing weekly group sessions and the need to evaluate alternative, self-directed behavior change


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methods to promote weight loss. Thus, we propose to evaluate the utility of RT-CGM, an emerging technology that holds promise as a behavior modification tool to promote weight loss and lifestyle changes in those with obesity, prediabetes or diabetes.

Several studies have demonstrated that encouraging patient engagement enhances self-care behaviors such as healthy eating (12-15). Patients are more likely to engage in healthy behaviors when they are given appropriate tools and are supported by their clinicians. For example, structured self-monitoring of blood glucose (SMBG) by 7-8 fingersticks a day has been shown to improve glycemic control in patients with diabetes by helping them understand glycemic response to food and activity (16). However, this is nearly impossible to reproduce in a real-world setting because of the inconvenience of performing SMBG and the discomfort associated with multiple fingersticks. The technology of CGM uses a tiny sensor inserted in the subcutaneous space to provide a simple and painless method of obtaining 288 glucose readings a day and needs only 2 fingersticks a day for calibration. There are two forms of CGM – blinded and real-time (RT). The former collects the blood glucose information but does not permit the person wearing the device to see a graphic display of their data. In contrast, RT-CGM provides the data on a smart phone for patients to view in real time and is thought to promote behavior change because the user gets real-time feedback about the effect of their food choices and exercise on glucose levels.

There are a multitude of reasons for the significance and innovation of this protocol. Without weight loss, 15-30% of people with prediabetes may develop Type 2 diabetes within five years(1). In patients with diabetes, as little as 5% weight loss may significantly improve glycemic control (30). It has been hypothesized in previous studies that RT-CGM causes behavior modification in both Type 1 and 2 diabetes but few if any studies have objectively demonstrated how RT-CGM causes behavior modification or its use as a weight loss tool. Because of its simplicity, RT-CGM could be used in community/primary care clinics where other more intensive and complex interventions for weight loss may not be available. It could also be used in the adolescent population with new onset Type 2 diabetes as a teaching tool for both the adolescent and family unit. This would be the first study that would evaluate RT-CGM as a behavior modification and weight loss tool in patients with either prediabetes or diabetes. The DPP educational materials have not been evaluated outside of the core 12 weekly in-person intervention sessions which are time-consuming and costly. This study would provide evidence that a modified DPP approach was effective when combined with RT-CGM. Previous RT-CGM studies in Type 1 and Type 2 diabetes have not used standardized educational lifestyle materials with CGM teaching, which could help create a practice model to use in primary care/community clinics.

## C. Preliminary Studies

Many studies have demonstrated that RT-CGM can be used in adults and children with both Type 1 and Type 2 diabetes resulting in improvement in HbA1c and/or a reduced frequency of hypoglycemia (17-19). Table 2 shows the average blood sugars of normal, prediabetic, and diabetic patients (24). Our initial research showed that the use of RT-CGM serially over 3 months improved HbA1c by an average of 1.0% in subjects with Type 2 diabetes on no prandial insulin (20). Nutrition and activity changes were not measured but the 3-month HbA1c improvement was sustained for another 9 months without further RT-CGM intervention (21). We hypothesized that the RT-CGM data motivated the subjects to make salutary changes in their diet and exercise habits leading to this long-term improvement in HgA1c (20, 21). However, there has been little direct examination of RT-CGM as a behavior modification/weight loss tool, as most studies have focused on HbA1c changes. Yoo et al. did show that intermittent use (3 days of RT- CGM every month for 12 weeks) produced a significant decrease in calorie

consumption, increase in physical activity, improvement of weight, and a 1% decrease in HbA1c in poorly controlled patients with Type 2 diabetes (22). Allen et al. found that the data from a single three-day session of blinded CGM when combined with subsequent counseling and review of the CGM glucose data with the patient resulted in an increase in physical activity and a decrease in HbA1c by 1.2% and BMI by 0.5 $kg/m^2$ (23). The only study using RT-CGM in patients with prediabetes showed significant glycemic variability at baseline but did not show decreased glycemic variability or improvement in weight after 6 months, and diet and activity levels were not measured (24, 25). The reasons for the failure to achieve weight reduction in that study may have been due to the lack of specific lifestyle counseling and/or instructions on use/interpretation of RT-CGM to the subjects. In addition, the rigorous RT-CGM schedule in the protocol (6 days of RT-CGM wear on 4 occasions over 3 months) may have been too intense for patients with prediabetes who are generally not even required to perform fingerstick blood glucose measurements.

In our original study on patients with Type 2 diabetes using RT-CGM, the mean, unadjusted HbA1c decreased by 1.0, 1.2, 0.8, and 0.8% in the RT-CGM group vs. 0.5, 0.5, 0.5, and 0.2% in the SMBG group at 12, 24, 38, and 52 weeks, respectively (P = 0.04). There was a significantly greater decline in HbA1c over the course of the study for the RT-CGM group than for the SMBG group, after adjusting for covariates (P < 0.0001, figure 1). Also, more people in the RT-CGM group experienced weight loss of >3 pounds in the 0- to 12-week time period compared with the SMBG group (*P* = 0.03, Table 1) (21). In the prediabetes study with RT-CGM significant glycemic variability (GV) was seen in prediabetes participants with Mean Amplitude of Glycemic Excursion: 50 +/- 18 mg/dL (24) as compared to other studies which showed excursions of 26-28 mg/dL in normal subjects and 75 +/- 28 mg/dL in patients with diabetes (31). However, the change in GV or weight loss was not significantly improved which was surprising as focus groups conducted after intervention were positive about the RT-CGM experience (25). Figure 2 is an example of a representative CGM tracing of a “normal” patient, a patient with prediabetes and one with diabetes. Behavior modifications were not evaluated in either the prediabetes or Type 2 diabetes RT-CGM study. The studies also did not assess whether blood sugars are affected by significant education about diet and exercise. We propose that further education on how to use RT-CGM will help facilitate weight loss and behavior modification. There are only two studies that have evaluated behavior modification changes in patients with Type 2 diabetes and none in the pre-diabetic population (see background above).


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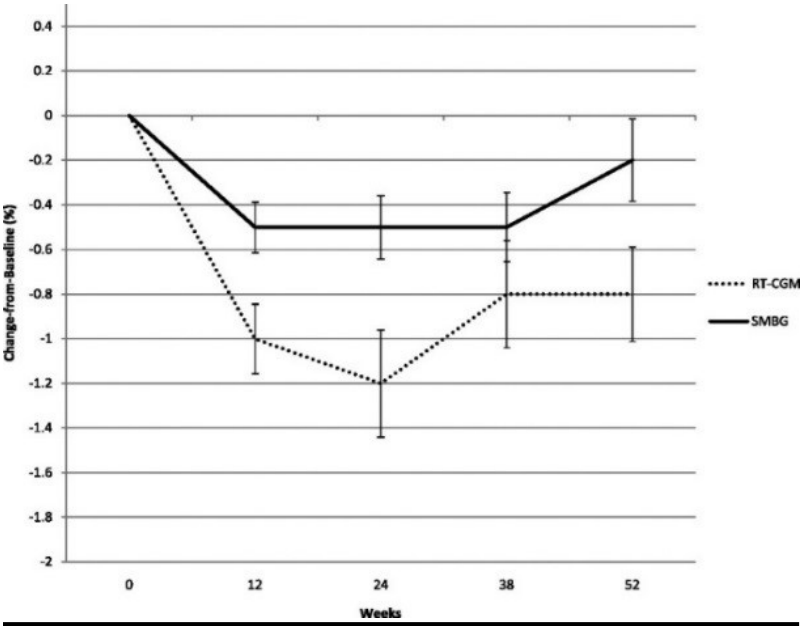



**Figure 1: Mean HbA1c change from Baseline**
Change equals later HbA1c minus baseline HgA1c. This figure shows the raw mean changes and SEMs A separate multilevel model of the actual HbA1c values, with a transformation of the time variable to reflect the deceleration of change over time (1/time$^2$, with time defined as 1–5), showed that the decline in A1c over the course of the study differed between the groups net of other factors known to cause A1c change: age, sex, diabetes therapy, and initiation of insulin(21).

| | 0–12 weeks | | | 0–52 weeks | | |
|---|---|---|---|---|---|---|
| | RT-CGM | SMBG | *P* | RT-CGM | SMBG | *P* |
| Weight loss (> −3 pounds) | 20 (40) | 9 (18) | 0.03 | 23 (46) | 17 (34) | 0.37 |
| No weight change | 24 (48) | 29 (58) | | 16 (32) | 15 (30) | |
| Weight gain (> +3 pounds) | 6 (12) | 12 (24) | | 11 (22) | 18 (36) | |

Data are *n* (%). *P* values are from $\chi^2$ tests.

**Table 1: Mean weight change by group CGM vs. SMBG** (21)

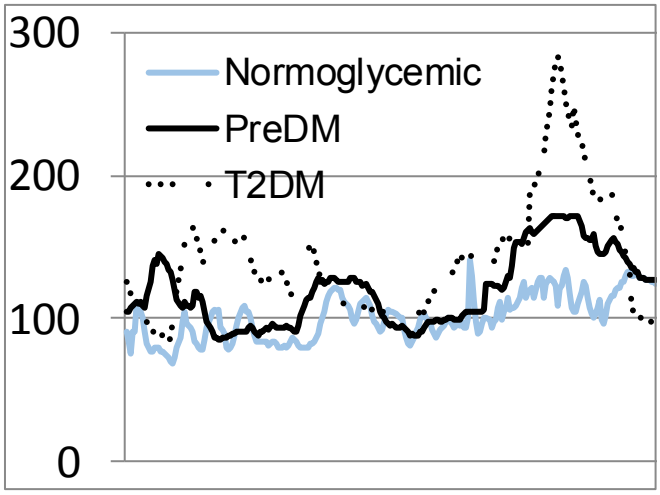



Figure 2: Representative Tracings of Patients with Prediabetes, Diabetes and Normal(24)

| Normal mg/dl +/- SD | PreDM mg/dl +/- SD | T2DM mg/dl +/- SD |
|---|---|---|
| 100.0 +/- 16.4 | 119.9 +/- 25.5 | 141 +/- 41.8 |

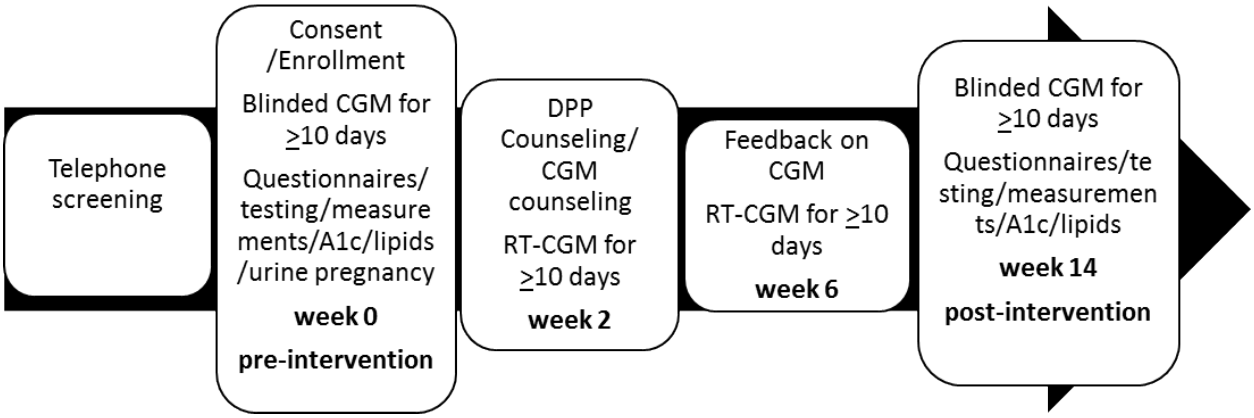
**Table 2: Average blood sugars of Patients with Normal, Prediabetes, Diabetes** (24)

## D. Research Design and Methods

The central premise of this intervention is that for RT-CGM to be effective as a behavior modification tool for weight loss in patients with prediabetes and diabetes it must include education on interpreting RT-CGM data in the context of appropriate initial lifestyle and weight reduction counseling. We are guided by Social Cognitive Theory, which specifies goal setting as an important strategy (26, 27). This approach has been widely used for understanding and researching behavior change. When specifically applied to nutrition education interventions it has been shown to be successful when the interventions are behaviorally focused and theory driven. Cullen et al. developed a goal-setting process, based on previous work to help dietitians use goal-setting strategies in nutrition counseling by: (1) recognizing a need for change; (2) establishing a goal; (3) adopting a goal-directed activity and self-monitoring; and 4) self-rewarding goal attainment (28, 29). We will follow a counseling protocol that was designed to change efficacy beliefs about diet and activity and follow this basic strategy. In the first session we will: (1) outline benefits of nutrition and activity as based on the DPP and discussed CGM patterns with each participant, i.e. the effect of food and activity on blood sugars; (2) set specific activity and calorie goals, and; (3) monitor with CGM. In the second session, we review and evaluate the CGM patterns and challenge the participants to improve their dysglycemic pattern (goal attainment). We have selected ten days' duration of RT-CGM over two sessions based on the limited previous studies and we anticipate this study will provide important insights on whether or not RT-CGM is effective as a behavior modification tool for weight loss in patients with prediabetes and diabetes.

A maximum number of 45 participants will be recruited that meet inclusion/exclusion criteria for the study. Recruitment information about the study will be made available to all medical personnel including medical assistants, nursing staff, and primary care providers at the

GW Medical Faculty Associates Internal Medicine clinic, Gynecology clinic, and Endocrine clinic by medical staff and provider flier (Appendix F). Information about the study will be made available to those patients by a Study Flier (Appendix H) which will provide them with contact information for the study coordinator. As well, if potential participants express interest in the study to medical staff at GW, permission for the study coordinator to contact them via telephone or email will be requested and potential participants will be contacted for further screening and potential enrollment. The Study Screening and research procedures will take place at the GW endocrine clinic. Subjects may also be identified through posters and flyers placed in the GW community. Potential subjects who satisfy the study criteria and express interest in the study will be given information about participation either by mail, email or a phone call, depending on their preference. Pre-screening questions will be asked but no study related procedure or screening questions will be performed until informed consent/authorization have been obtained (see Appendices D and L).




We propose to perform a prospective study of 45 participants that will involve 15 subjects (ages 18-55) who are obese (BMI>30) and have prediabetes with HbA1c 6.0-6.4%, and 15 obese (BMI>30) subjects with Type 2 diabetes (ages 18-55) and with HbA1c 7.0-10.0%. 15 subjects will be in the control group with either prediabetes (n=7) or diabetes (n=8). Subjects will be randomized to intervention or control through a computer-generated system. All eligible participants will be able to walk 2 city blocks at baseline. Patients with prediabetes will be on no medications for diabetes and patients with Type 2 diabetes will have to be on the same diabetes medication(s) for 3 months prior to enrollment. The medication regimen may include basal insulin but not premeal insulin. Uncontrolled diabetes A1c>10.1% will be excluded, as well as participants who are pregnant, lactating, enrolled in another weight loss program, or using a weight loss medication (see inclusion /exclusion criteria below). The study will be advertised by flyers in the GW Endocrine Clinic, Internal Medicine Clinic, and also advertisements in the local newspaper.

**Inclusion criteria**:
1. Age 18-55
2. Prediabetes (A1c 6.0-6.4) or Diabetes (A1c 7.0-10)
3. BMI ≥ 30 kg/m2
4. Willing to wear pedometer during study period
5. Able to walk 2 city blocks at baseline without assistance (self-reported)
6. Reading level at least 6$^{th}$ grade in English
7. Expected to remain in local community for at least 4 months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8. Either is not treated with or has been on a stable treatment regimen of any of the following medications for a minimum of 3 months prior to Visit 1 (Screening/Enrollment):
    a. Sulfonylureas
    b. Biguanidine
    c. Thyroid replacement therapy
    d. Glp-1 agonists
    e. Sodium-glucose co-transporters
    f. Basal insulin
    g. Thiazolidinediones
    h. Hormone replacement therapy (female subjects) estrogen/progesterone products
    i. Oral contraceptives/birth control (female subjects)
    j. Antidepressant agents (SSRIs, Paxil, Prozac, Celexa, Zoloft, etc.)

9. Is able to read, understand, and sign the Informed Consent Form (ICF) and if applicable, an Authorization to Use and Disclose Protected Health Information form (consistent with Health Insurance Portability and Accountability Act of 1996 [HIPAA] legislation), communicate with the investigator, and understand and comply with protocol requirements

**Exclusion criteria:**

1. Women who are pregnant, lactating, planning to become pregnant
2. Subjects who are taking amphetamines, anabolic, or weight-reducing agents
3. Contraindications to moderate exercise
4. Pre-prandial insulin
5. On any antipsychotic medication or history of schizophrenia or bipolar disorder
6. Daily use of any form of steroid medication (oral, inhaled, injected) within the last 3 months
7. Active wounds or recent surgery within 3 months
8. Inflammatory disease, or chronic and current use of anti-inflammatory drugs or narcotics
9. Active cardiovascular diseases within 12 months of Visit 1, such as myocardial infarction, clinically significant arrhythmia, unstable angina, coronary artery bypass surgery, or angioplasty; or are expected to require coronary artery bypass surgery or angioplasty during the course of the study
10. Presence or history of severe congestive heart failure (New York Heart Association Class IV [CCNYHA 1994])
11. Has evidence of current abuse of drugs or alcohol or a history of abuse that, in the investigator's opinion, would cause the individual to be noncompliant
12. Enrolled in another weight loss program
13. Already receiving continuous glucose monitoring (CGM)

Interested volunteers will be screened by telephone or in person in respective clinics and then scheduled for a screening visit week 0). If potential participants express interest, they will be provided an email address or phone number to call for more information. Alternatively, participants will be asked if they would like to be called to receive more information and are willing to provide their contact information to study staff. If after receiving more information, the potential participant is interested, then pre-screening questions (appendix D) will be asked.If still eligible, then a screening appointment will be arranged by study staff. If the participant is not interested in participating, a handout will be given for other sources for weight loss.

**Study Design (see Appendix C):**


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**Screening/Pre-Intervention Visit:**

Consent will be obtained prior to any screening procedures being completed, and conducted in a quiet room. Participant will be given ample time to ask questions, and a copy of the signed consent form will be given prior to start of screening visit.. Participants will fill out a contact form, including emergency contact. Study staff will review medical history and medications (through appendix E), as well as all inclusion/exclusion criteria. Vital signs will be collected, including height, weight, blood pressure, waist circumference, and resting heart rate. Body composition will also be assessed by bioelectrical impedance using a Tanita scale. A urine pregnancy test (if applicable), lipid panel, and HbA1c, both point of care (fingerprick) and serum, confirmed via LabCorp, will be obtained to determine prediabetes or diabetes. Approximately 1 teaspoon of blood will be drawn. (Note: 10 hour fasting labs will be required for Weeks 0 and 14. If the patient is not fasting, they can return the next day for fasting labs.) If a patient has an HbA1c documented in the medical record within 2 weeks of the pre-intervention session, then the point of care HbA1c will not be done. The available A1c will be used. If they meet all inclusion and exclusion criteria (as outlined above), they will be randomized into either the CGM intervention or control arm at the screening visit.

At the pre-intervention session (week 0) the control and CGM intervention groups (composed of both diabetics and prediabetics) will be asked to wear the CGM blinded for 10 days. They will be asked to continue their usual diet and activity and observe and record their physical activity and food intake on appropriate logs. They will be given a pedometer to track physical activity data, and be given other self-report questionnaires on their perception of CGM, physical activity, and nutrition. The 3-minute stair step test will be conducted. Week 0 consenting and baseline data/measurements will take between 1 hour 30 minutes to 2 hours.

**Weeks 2, 6**

RT-CGM education and use will be coupled to one initial nutrition and exercise counseling session at Week 2 by the diabetes educator. Individually administered nutrition and exercise counseling will be based on a condensed version of the standard 12-session Diabetes Prevention Program Group Lifestyle Balance (DPP GLB, Appendix B) material and received by all participants. All those enrolled in the CGM intervention (N=30) will participate in 2 cycles of RT-CGM with direct feedback on CGM patterns at the second session, Week 2.

Both groups will then follow up and be given diet and exercise education handouts and instruction based on the DPP GLB core nutrtion and physical activity materials (Appendix B) at Week 2. The diabetes and prediabetes CGM intervention groups will also receive additional education on how food and exercise affects bloods sugar, and how to evaluate and respond to their blood sugar changes with RT-CGM (Appendix A). The CGM intevention participants will then wear the RT-CGM device for 10 days at week 2 and at 6 weeks. At week 2, CGM patterns will be reviewed with diet and food logs, and CGM intervention patients will be challenged “to beat their averages. The control group will review their diet and exercise log with the instructor and attempt to continue to make small changes in diet and exercise. Vital signs will be taken at each visit, including waist circumference. Pedometer data will be collected at weeks 6 and 14. Week 2 education on nutrition and RT-CGM will take 1 hour 30 minutes to 2 hours. Week 6 CGM review and measurements will take 1 hour. They will mail their sensors back from the continuous glucose monitoring device after 10 days, along with physical activity and food logs. They continue wearing their pedometers during this time.


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**Week 14**

All groups will wear blinded CGM for 10 days, starting at the 14 week visit, and their pedometers. Lipids and hemoglobin A1c will be obtained. Hemoglobin A1c will again be checked through fingerprick in the clinic, and also through serum to LabCorp. Approximately 1 teaspoon of blood will be drawn at that time also. Vital signs will be collected, including height, weight, blood pressure, waist circumference, and resting heart rate. Body composition will also be assessed by bioelectrical impedance using a Tanita scale. Participants will be given other self-report questionnaires on their perception of CGM, physical activity, and wellness. Food and physical activity logs will be reviewed. The intervention group will complete questionnaires on their perception of CGM. Week 14 data collection will take 1 hour 30 minutes. Participants will mail back their pedometers, the sensors from their continuous glucose monitoring device after 10 days, and physical activity and food logs.

**Study Procedures**

**Medical Device/CGM/ DEXCOM G6:** CGM is a way to measure glucose levels in real-time throughout the day and night. A tiny electrode called a glucose sensor is inserted under the skin by a skin prick to measure glucose levels in tissue fluid. A small plastic piece of tube remains inserted in the skin. Typically you cannot feel this tubing once inserted. It is connected to a transmitter that sits on top of your skin and is about the size of a quarter. It is attached/secured by medical tape to your skin. It is approved for use on the abdomen for 10 days. It either records the sugars which we then download in our clinic (blinded part of the study) or it sends the information via wireless radio frequency to a monitoring/ display device or to a cellular phone so you can see your own data on your sugars. DEXCOM G6 is FDA approved for use in patients with diabetes and will be used in accordance with instructions as approved for diabetes. It is not currently an approved indication for patients with prediabetes, but will be used in accordance with instructions as approved for diabetes. The risk is minimal with this device use. In this study, we recommend patients connect this to their cell phones, but if not, we will provide transmitters for them for real-time monitoring. Study staff will insert the sensor, and then the patients pull off the sensor themselves after 10 days, and mail back to the study team.

**Diabetes Prevention Program Educational Materials (see Appendix B):** The DPP Group Lifestyle Balance™ (GLB) Program is a comprehensive lifestyle behavior change program adapted directly from the successful lifestyle intervention used in the National Institutes of Health funded Diabetes Prevention Program (DPP). The original individually administered DPP Lifestyle Balance intervention (copyright 1996; 2011) was developed and written at the University of Pittsburgh by the DPP Lifestyle Resource Core on behalf of the DPP Research Group and consolidated into 12 sessions designed to be administered weekly and potentially given by laypeople (32). Complete information about DPP is available at: https://www.diabetesprevention.pitt.edu/index.php/for-the-public/for-health-providers/group-lifestyle-balance-curriculum. In this study, we will offer an adapted brief-intervention DPP in the first meeting. Our intent in providing this material is to support a primarily *self-directed* diet, activity and weight behavior modification context for use of the RT-CGM. Our diabetes educator will be responsible for reviewing the DPP materials and fat, calorie and activity goals at their original session along with materials developed about what different foods and activity does to your blood sugars prior to the initial use of RT-CGM. We reviewed the educational materials and handouts from the 12 sessions and consolidated them into a 12 page handout which was also reviewed by the current director of The Diabetes Prevention Support Center/DPP Lifestyle Resource Core at the University of Pittsburgh. Consistent with social cognitive theory, all participants are given fat and calorie goals based on their initial weight upon enrollment and an


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activity goal of 150 minutes of activity weekly with ongoing goal to 300 minutes weekly. They are asked to self–monitor weight, food intake and physical activity levels with goal of 7% weight loss (32).

**Measurements (Appendix C)**: We will measure HbA1c at the beginning of the study period and at 14 weeks. At each visit, blood pressure, weight, height, and waist circumference will be measured. At baseline and 14 weeks, questionnaires on diet and physical activity and self-perception questionnaires will be obtained. In the intervention group at 14 weeks, a questionnaire about CGM technology and perception of benefit of CGM use will be obtained, for diabetics and for prediabetics. Body composition will also be assessed serially by bioelectrical impedance using a Tanita scale at baseline and 6 weeks and 14 weeks. Pedometer data will be downloaded at 2 weeks, 6 weeks and 14 weeks. Physical fitness testing by resting heart rate and three minute stair step (amount of/change in steps climbed in 3 minutes) will also be obtained at baseline and 14 weeks.

**Anthropometrics: Height** will be recorded in centimeters and inches by a Stadiometer. **Weight** will be recorded in pounds and kilograms using a SECA Digital scale. **Waist circumference** will be meaured using a flexible measuring tape, and **blood pressure** taken with an Omron Professional Digital blood pressure machine.

**Bioelectrical impedance**: This will be collected with the Tanita Body Composition Machine. We will acquire body fat %, total body water %, fat free mass and more, in addition to BMI. To gather these measurements, subject's height and age are inputted into the machine, and subjects stand on the scale with bare feet. These values provide a better picture than simply weight and BMI of the overall subject's body composition.

**Food and Physical Activity Logs (Appendices M and N):** Participants in both groups will record their daily food intake and physical activity in these logs throughout the study. They will return these logs by mail for reviewing for 10 days after each study visit.

**Physical Activity Measurements:**
**Resting heart rate:** Participants will remain in a seated position for a miminium of 15 minutes prior to resting heart rate being taking with a Omron Professional Digital blood pressure and heart rate monitor.

**Three minute stair step**: Queens College Step Test**:** The Queens College Step test is one of many variations of step test procedures, used to determine aerobic fitness. Compared to the Harvard Step Test, this version has a lower step height, slower cadence, shorter test and more simple analysis (33).

**Pedometer data**: We will compare average steps per week at 14 weeks relative to baseline steps assessed in the first 2 weeks. After 14 weeks, we will assess the percentage of participants that attain a weekly goal of 10,000 steps daily for greater than 3 out of 7 days of the week. While we know of no validated reference for this, this goal was discussed with Peter Kokkinos, PhD, FAHA, FACSM who is Director, Human Performance Research & Lifestyle Interventions for Veterans (LIVe) Veterans Affairs Medical Center, DC.

**Nutrition/Activity Questionnaires (Appendix I)**: Starting The Conversation (STC) is an eight-item simplified food frequency instrument designed and validated for use in primary care and


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health-promotion settings (34).

**Physical activity (Appendix J)**: The International Physical Activity Questionnaire (short) is a validated questionnaire that reviews the last 7 days of activity for middle aged adults (age 15-69 years) (35).

**Collection of Human Biological Specimens**:
**Fingerstick and serum HbA1c**: The HbA1c test is a blood test that provides information about a person's average levels of blood glucose over the last 3 months. The DCA Vantage Analyzer HbA1c assay tests for a quantitative determination of HbA1c in human whole blood, and provides immediate test results from a finger prick of blood. Serum HbA1c is sent via LabCorp.
**Urine HCG:** HCG by urine dipstick will be collected prior to enrollment in study, if applicable.
**Serum fasting lipids** will be collected at baseline and 14 weeks. This data will be provided to the participant to discuss further with their physician at the completion of the study when both pre and post labs are available.

**Perception of CGM (Appendices Q and R):** The Harvard Joslin Diabetes Center has developed a series of questionnaires on CGM experiences, opinions and expectations that will be given at the end of the intervention and has been adapted for the prediabetes population as well.

**CGM Data /Evaluation Measures:** Compliance/duration of participants with wearing CGM will also be recorded. Glucose dynamics, e.g., standard deviation, mean amplitude of glucose excursion (MAGE), and other statistical measures of glucose variability in those with pre-diabetes/diabetes/obesity with be reviewed from the CGM device data at baseline 2, 6 and 14 weeks

**Self perception/psychosocial questionnaires (Appendix K):** The Weight Efficacy Life-Style Questionnaire (WEL), Eating Habits and Exercise Confidence questionnaires will be given to patients at the beginning and end of the study to help evaluate any changes in self-perception after intervention (36-38).

## F. Risks and Side Effects:

There are various possible risks and side effects that a participant may incur as a result of this study. At the beginning of the study, when participants are administered the informed consent form by research staff, they will be informed that their participation is completely voluntary and will be informed of the risks and benefits. They are free to leave the study at any time and will not be penalized. Potential subjects will also be told that failure to participate in no way affects the usual care they would receive from their primary care provider. Only after all questions have been answered, both study staff and the participant will sign and date the consent form.

It is very unlikely that there will be any adverse event from the lifestyle intervention except possible musculoskeletal injury from increased physcial activity, but this will be mitigated as participants will be taught how to gradually increase their activity goals. Typically, musculoskeletal soreness and discomfort is minimal and temporary. The risks associated with exercise occur occasionally (1-10% or 1-10 people in 100) and include fatigue, muscle soreness, and injury such as sprained ankles or pulled muscles (39). Risks are reduced by proper warm-up and cool-down periods.


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There may be additional risk of heart problems for those who have a chronic disease or experience symptoms with exercise, although this risk is extremely minimal given the intensity of the recommended exercise, i.e., brisk walking or jogging in a young population. The level of activity that we will recommend for participants is thought to be more helpful than harmful, but there is a very small risk of heart attack or sudden death during exercise. Heart attack has been estimated to occur less than once out of 500,000 hours of exercise in people without known heart disease (40). The risk is greater in people with heart disease. It is important that participants contact their physician if they develop diabetes, heart disease or other related health problems during this study.

Modest weight loss is also associated with a few risks. It is common or likely for participants to experience hunger, lightheadedness, and/or constipation when reducing their calorie intake. However this program recommends a healthy balanced diet, rich in plant based foods, and a regular pattern of meals and snacks (consistent with national dietary recommendations), which may reduce this risk.

There are possible risks associated with the intervention activities, including the medical device, including:

Rare but serious (Event Rate < 1%): Potential to unmask heart disease

- Less Likely (1% ≤ Event Rate < 5%): CGM site infection or tape allergy (<1-2%) (41)
- Likely (5% ≤ Event Rate < 10%): sports injury such as ankle sprain, knee pain from increased physical activity.
- More likely (Event Rate ≥ 10%): None

There may be temporary discomfort with the device at insertion time. That can include bruising or redness of the skin, rare allergic reaction to the taped use to keep device in place, infection at site, and potential perceived dislike of having medical device on body for 10 days.

Participants may experience side effects from the fingerstick blood prick. There may be temporary discomfort including possible bruising or redness of the skin, lightheadedness, and on very rare occasion infection. People may experience embarrassment associated with measurements of weight and waist circumference. Minor discomfort may be experienced when answering questions that are personal in nature. Participants may have some lightheadedness or imbalance with the stair step test. Muscle strain or soreness are a rare risk of injury or joint discomfort with any the physical function tests. After demonstration by staff, if participants feel that the stair step test may be unsafe, they may choose not to do them.

There is a rare risk that a breach of confidentiality could occur; however, every effort is made to prevent this from happening. In addition, every effort is made to perform assessment activities in a private and respectful manner by research staff who have been specifically trained to do them.

## G. Benefits:

Participants will likely receive no direct benefit from these measurements beyond receiving notification of their results. However, they may receive benefit from the lifestyle intervention activities. Participants may lose weight and/or reduce the level of one or more diabetes/heart disease risk factors if prediabetic and improve diabetes control if tjeuhave diabetes. This research may benefit society by enhancing our understanding of medical devices that may help improve lifestyle modifications and thus help establish new procedures and practices that are associated with reduced risk for diabetes and heart disease. This could also lead to improved health and well-being, and weight overall in adults.

## H. Conflicts Of Interest:

No conflicts of interest are noted.

## I. Confidentiality:

All of the subjects' personal information, clinical data and consent documents will be stored in a secure location in a locked file cabinet in the George Washington University Endocrine clinical research coordinator's office. The subjects' personal information and research related clinical data other than routine laboratory results will be accessible only to the Principal Investigator and the research staff associated with the study. Organizations that may inspect and copy your information include the IRB, The GeorgeWashington University. A master code linking the unique study numbers with subjects' identifying information will be kept by the Principal Investigator or by the Project Officer in a locked file cabinet. Additionally all data collected by coordinators will be entered and managed through the encrypted Research Electronic Data Capture (REDCap) system maintained at George Washington University/Children National Medical Center (CNMC). All data is deidentified with no personal health information entered (PHI). REDCap was developed specifically around HIPAA security guidelines. REDCap has been disseminated for local use at more than 940 other academic/non-profit consortium partners in 75 countries. REDCap servers are housed in a local data center at CNMC, and all web-based information transmission is encrypted. This system is accessed through a secure login and password. Only the RedCap database coordinators and study staff will have access privileges to the George Washington data set and will be strictly prohibited from sharing passwords. All will undergo the standardized authorized training provided by the RedCap team. Staff will maintain files in password-protected documents on HIPAA-compliant servers. REDCap programmers build in quality controls for the data that will be collected according to their stringent protocols. Data will be stored for 3 years after study completion for possible re-analysis and sub-group analysis that the clinical team may determine to be useful. More information about the consortium and system security can be found athttp://www.projectredcap.org. Dr. Ehrhardt and her research team will destroy the informed consent, research source documents, data files, and master code 3 years after the completion of the study. This will allow time for the PI and collaborators to reexamine the data as needed in the revision process for manuscripts submitted to peer-reviewed journals.

All information that the study subjects provide study personnel is for research purposes only and, as such, names and any other identifying information will not be reported or published in papers, presentations, or proposals that result from this research.

When the subject enrolls in the study, she/he will be assigned a unique study number that is not any part of his social security number or other personal identifier. These unique study numbers will be used to identify all information that subjects provide and any information that is collected from their medical records. The unique study numbers will be assigned sequentially according to the order of study enrollment and if they have diabetes (DM) or prediabetes (PDM). Subjects will be identified by the initials of the group to which they are randomized and 3 numbers according to their entry into the study beginning with 001. Therefore, the first subject randomized to the DM group willl be DM-001 and the first subject randomized to the PDM group will be PDM-001. A total of 22 PDM and 23DM subjects will be enrolled.

Although every precaution is being taken to protect participant privacy, breach of confidentiality is always possible. In the unlikely event of a breach of confidentiality, the nature of the research data is not of a sufficiently personal nature to negatively affect employment status, lead to civil/criminal liability, incur financial risks to the study participants, or other risks.

## J. Subject Compensation:

Participants will be given $25 upon completion of each visit and an additional $50 dollars upon return of the CGM device at the end of study, for a total of $150. Nutrition and exercise counseling sessions will be provided for free. Subjects will also have use of the medical device during the study for free. No additional cost will be incurred by subjects. Participants will be asked if they would like to receive additional information about alternative resources for weight loss in the community (Appendix G).

## L. Appendices

A. Real-Time Continuous Glucose Monitoring educational material

B. Diabetes Prevention Program Core Teaching educational material

C. Table of Study Measurements

D. Pre-Screening Checklist

E. Medical History and Screening Form

F. Medical Staff and Provider Flier

G. Alternative Resources for Weight Loss

H. Participant Study Flier

I. Nutrition/Food Questionnaire

J. Physical Activity Questionnaire

K. Weight and Activity Lifestyle Questionnaire/Wellness Perception Questionnaire

L. Phone Script for Pre-Screening

M. Fitness Log

N. Food Log

O. Adverse Events Log

P. References

Q. Continuous Glucose Monitoring Perception Questionnaire - Diabetes

R. Continuous Glucose Monitoring Perception Questionnaire - Prediabetes


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