Study Protocol

TITLE: Perioperative Stress Hyperglycemia in General and Vascular Surgery Patients

NCT NUMBER: NCT04862234

Protocol Date: October 8, 2024

PROTOCOL TITLE: Perioperative Stress Hyperglycemia in General and Vascular Surgery Patients: An Observational and Randomized Controlled Pilot Trial.

Protocol Number: IRB00097659

National Clinical Trial (NCT) Identified Number: 04862234

Principal Investigator: Georgia M. Davis, MD

Funding Source: National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

Version Number: v.6.0

08.06.2024

Summary of Changes from Previous Version:

Revision #	Version date	Summary of changes
	7/27/2017	**Initial Protocol**
1	**12/10/20**	**Update PI, add observational study arm**
2	**1/20/21**	**Biomedical protocol format change**
3	**6/15/21**	**Updated phlebotomy collection procedure and participant payment schedule**
4	**12/20/21**	**Updated the recruitment methods to include Telehealth patients.**
5	**3/17/2023**	**i. Changed inclusion criteria for study participants from BMI ≥30 kg/m2 to 28 kg/m2** **ii. Add Hemoglobin <10 gm/dL to exclusion criteria for Aim1.**
6	**8/6/24**	**Removal of Clinical Trial procedures (Aim 2) and replacement with Updated Aim 2.** **Includes updated DSMB meeting schedule changed to every 6 months.**

7	**10/08/24**	**Accommodate surgical procedure rescheduling timeline**

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1. Study Summary

Study Title	Perioperative Stress Hyperglycemia in General and Vascular Surgery Patients: An Observational and Randomized Controlled Pilot Trial
Study Design	Observational Cohort (Aim 1, updated Aim 2), RCT (Aim 2)
Primary Objective	**Aim 1:** To fully characterize preoperative glycemic control and prospectively determine clinical, metabolic, and inflammatory biomarker profiles associated with stress hyperglycemia. **Aim 2:** To conduct a randomized controlled pilot study to determine if single dose administration of dulaglutide can improve perioperative glycemic control in high-risk subjects. **Updated Aim 2:** To determine patterns of preoperative glycemic control by CGM that are associated with SH.
Secondary Objective(s)	**Aim 1a:** To examine clinical, metabolic and inflammatory biomarker characteristics associated with SH in individuals at high risk for dysglycemia undergoing general and vascular surgery. **Aim 1b:** To determine the timing, duration, and severity of SH by CGM and its association with alterations in inflammatory/oxidative stress biomarkers. **Aim 1c:** To explore the relationship of the duration and severity of SH with perioperative complications. **Aim 2:** To conduct a randomized controlled pilot study to determine if single dose administration of dulaglutide can improve perioperative glycemic control in high-risk subjects. **Updated Aim 2a:** To identify preoperative CGM profiles associated with postoperative SH **Updated Aim 2b:** To compare the predictive value of preoperative CGM profiles with traditional metrics of underlying dysglycemia.
Research Intervention(s)/Interactions	Administration of oral glucose tolerance test (Aim 1) Administration of dulaglutide vs placebo (Aim 2) Continuous glucose monitor placement (Aim 1, Aim 2, updated Aim 2)

Study Population	Patients without a known history of diabetes with known risk factors for dysglycemia (age >45 years, BMI ≥28 kg/m^2) undergoing general or vascular surgery.
Sample Size	165
Study Duration for individual participants	Up to 14 days (depending on length of hospitalization)
Study Specific Abbreviations/ Definitions	CRC: clinical research center CGM: continuous glucose monitor DM: diabetes mellitus GLP-1 RA: glucagon-like peptide-1 receptor agonist OGTT: oral glucose tolerance test SH: stress hyperglycemia
Funding Source (if any)	NIH/NIDDK

2. Objectives

Stress hyperglycemia, defined as a blood glucose >140 mg/dl in hospitalized patients without a prior history of diabetes mellitus (DM) is associated with increased risk of complications and mortality compared to patients with normoglycemia and with known history of DM. The underlying pathophysiology remains un-explored. Increased counterregulatory hormones (cortisol, glucagon, epinephrine, growth hormone), free fatty acids, inflammation and oxidative stress are likely involved in the pathogenesis of impaired insulin secretion and action leading to stress hyperglycemia.

However, no prospective studies have comprehensively examined preoperative glycemic control profiles and their association with the incidence, clinical predictors and underlying mechanisms of SH in general surgical patients. Accordingly, we propose a prospective study investigating clinical, metabolic and inflammatory/oxidative stress biomarker profiles leading to SH. We will use continuous glucose monitoring (CGM) technology to fully characterize the onset, duration and severity of SH during the perioperative period.

Given the association between stress hyperglycemia and poor hospital outcomes, our initial second aim was to determine if the prevention of stress hyperglycemia is feasible with the single administration of a weekly glucagon-like peptide-1 receptor agonist (GLP-1 RA), a common medication used to treat patients with established diabetes. We also planned to explore the role of beta-cell function, insulin resistance, and inflammation on the pathogenesis of stress hyperglycemia. However, given safety concerns regarding administration of GLP-1 RA medications in the perioperative period, enrollment for this aim was discontinued prior to study completion.

There is increasing data surrounding the utility of CGM in identifying underlying dysglycemia by characteristic glucose control patterns and associations with longer term clinical outcomes (e.g. development of diabetes, cardiovascular risk). To our knowledge, there is no current data on how CGM may be used to determine perioperative dysglycemia risk in patients without

diabetes. We will analyze preoperative CGM data to better define pre-existing glycemic control patterns (profiles) associated with the development of SH. The predictive capability of CGM profiles will be compared to traditional assessments of dysglycemia (e.g. OGTT, HbA1c).

The goals of this study are to: 1) conduct an extensive analysis of preoperative glycemic control and its relationship to clinical, metabolic and biomarker profiles of SH in a high-risk population, and 2) conduct a pilot randomized controlled trial to prospectively determine if single dose use of dulaglutide can improve perioperative glycemic control compared to insulin administration (standard-of-care) [DISCONTINUED], and 3) determine how preoperative CGM data profiles may be utilized to identify unique groups at risk for SH [UPDATED AIM 2]. Patients qualifying for the study will be approached at their preoperative clinic visit and invited to participate in the prospective observational study arm (Aim 1 and updated Aim 2). Prior to discontinuation, patients were invited to participate in the interventional trial for prevention of SH with dulaglutide (Aim 2) if they met inclusion criteria based on oral glucose tolerance testing (OGTT) or lab testing performed for Aim 1. Within 72 hours prior to planned surgery, consented patients will present to the clinical research center (CRC) to undergo evaluation with OGTT and lab testing with CGM placement. Previously, those patients with OGTT or lab results consistent with a diagnosis of prediabetes or newly diagnosed diabetes were asked if they would like to participate in Aim 2. Patients consenting to participate in Aim 2 were randomized to receive a subcutaneous injection of dulaglutide 0.75 mg or placebo during the CRC visit. Blinded CGM will be used to follow glycemic control parameters postoperatively during surgical admission. In addition to the above, baseline and postoperative levels of serum inflammatory and oxidative stress markers will be obtained to provide further information regarding beta-cell function and insulin resistance in relation to the development of stress hyperglycemia.

Data from this study will help to understand the underlying mechanisms leading to stress hyperglycemia and explore if dulaglutide and other GLP-1 RA may help prevent stress hyperglycemia in surgical patients. We will also explore characteristic CGM patterns indicative of SH risk in non-diabetic patients undergoing general surgery.

<u>Aim 1:</u> To fully characterize preoperative glycemic control and prospectively determine clinical, metabolic, and inflammatory biomarker profiles associated with SH.

1a. To examine clinical, metabolic and inflammatory biomarker characteristics associated with SH in individuals at high risk for dysglycemia undergoing general and vascular surgery. We will conduct a prospective cohort study in patients without a known history of DM with known risk factors for underlying dysglycemia (age >45 years, BMI ≥28 kg/m^2)[1,2] undergoing major general or vascular surgery. We will analyze pre- and postoperative clinical, metabolic and inflammatory biomarkers to determine profiles predictive of SH (glucose >140 mg/dL), create a risk stratification model, and explore potential mechanisms of SH.

1b. To determine the timing, duration and severity of SH by CGM and its association with alterations in inflammatory/oxidative stress biomarkers. Enrolled patients will have a CGM sensor placed preoperatively and continued during surgical hospitalization to monitor glucose levels. CGM data will be analyzed for the degree of hyperglycemia, time in target glucose range (70-140 mg/dL) and time in hyperglycemia (>140 mg/dL).

1c. To explore the relationship of the duration and severity of SH with perioperative complications. CGM data as above will be analyzed and correlated with data on a composite of hospital complications to determine associations between SH and postoperative outcomes.

Hypothesis: *We hypothesize that individuals with preoperative dysglycemia, including reduced insulin secretion and sensitivity, and altered inflammatory/oxidative stress markers will be more likely to develop SH. Those with high-risk profiles will experience more severe and prolonged SH, and a higher risk of complications.*

Aim 2 [DISCONTINUED]: To conduct a randomized controlled pilot study to determine if single dose administration of dulaglutide can improve perioperative glycemic control in high-risk **subjects.** We propose a pilot, randomized, placebo-controlled trial to include 80 high-risk subjects identified in Aim 1 with OGTT and/or HbA1c results indicative of pre-DM or DM.

Hypothesis: *We hypothesize that treatment with dulaglutide will improve the time within the optimal glucose range during the perioperative period in high-risk individuals with prediabetes and newly diagnosed diabetes.*

Aim 2 [UPDATED]: To determine patterns of preoperative glycemic control by CGM that are associated with SH.

a) **To identify preoperative CGM profiles associated with postoperative SH.** Short-term (<2 weeks) preoperative CGM data will be used to define and classify CGM profiles indicative of different levels of SH risk. Preoperative CGM data will be analyzed using CGM metrics (e.g. time-in-range [TIR, 70-140 mg/dL], GV) and machine learning methods to identify characteristic glycemic control patterns.
b) **To compare the predictive value of preoperative CGM profiles with traditional metrics of underlying dysglycemia.** Performance of CGM profiles in estimating postoperative SH risk will be compared to the performance of OGTT and HbA1c results obtained in Aim 1.

Characterization of preoperative CGM profiles predictive of SH will provide a novel and practical method for identification of high-risk patients and guidance for glucose monitoring in the perioperative period.

3. Background/Significance

Inpatient and perioperative stress hyperglycemia: Approximately 30% of non-diabetic patients undergoing surgery will develop stress hyperglycemia (BG >140 mg/dl) with most of them requiring insulin therapy during the perioperative period.[3-7] Previous studies indicate that the development of stress hyperglycemia in non-diabetic patients is associated with worse clinical outcomes when compared to patients with a known history of DM.[8-14] In patients undergoing general surgery, stress hyperglycemia is associated with up to a 4-fold increase in complications and a 2-fold increase in death compared to patients with normoglycemia.[1,15,16]

Our preliminary data through a retrospective database analysis of glycemic control and hospital outcomes in 1,971 consecutive patients with preoperative normoglycemia (preoperative BG<140 mg/dl) at 4 university-affiliated hospitals showed an increase in hospital complications (Figure 1) and mortality (Figure 2) in patients developing stress hyperglycemia. Of them, 415

patients (21%) developed ≥ 1 episode of BG 140-180 mg/dl and 206 patients (10.5%) had a BG > 180 mg/dl within 48 hours after surgery. Compared to patients with normoglycemia, patients with stress hyperglycemia had a longer length of hospital stay (LOS) and significantly higher rates of complications and mortality (all, p<0.001). After adjusting for age, gender, BMI, race and Charlson comorbidity score, compared to patients with normoglycemia, those with postoperative BG 140-180 mg/dl had higher odds ratios (OR) for both complications [1.68 (1.15 – 2.44)] and mortality [1.72 (0.42-7.1)]. The OR for complications and mortality in patients with postoperative BG >180 mg/dl were 3.46 (2.24-5.36) and 6.56 (2.12-20.27), respectively. These data emphasize the importance of gaining further understanding into the pathophysiology of stress hyperglycemia, as well as how its prevention may lead to improvement in hospital outcomes.

Figure 1. Unadjusted and adjusted composite of complications in stress hyperglycemia.

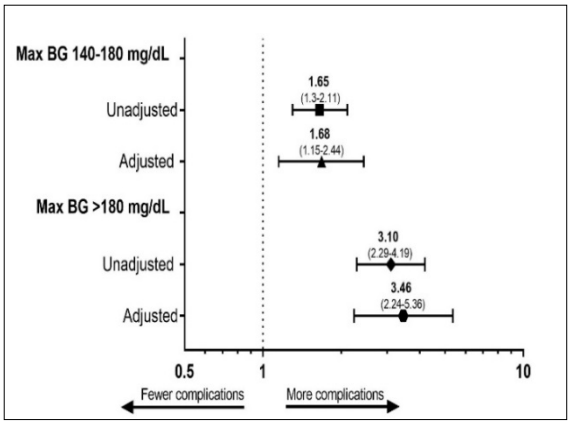
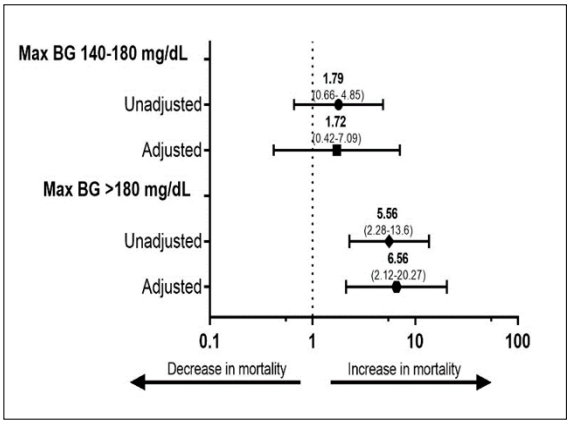


Figure 2. Unadjusted and adjusted mortality rates in stress hyperglycemia.



Mechanisms of Stress Hyperglycemia: Several contributing factors are known to favor the development of hyperglycemia in the hospital; however, its underlying pathophysiology remains un-explored. Acute illness raises levels of counterregulatory hormones (cortisol, glucagon, epinephrine, growth hormone), which increases hepatic glucose production, [17,18] diminishes insulin action in peripheral tissues and results in relative insulin deficiency[17-19] leading to hyperglycemia. Counterregulatory hormones in the setting of stress leads to enhanced lipolysis and increasing fatty acid (FFAs) concentrations [20,21] that leads to a dose-dependent **insulin** resistance in peripheral tissues [22] and increase hepatic glucose output. [23,24] Furthermore, hyperglycemia leads to generation of reaction oxygen species (ROS), lipid peroxidation, elevated cardiovascular inflammatory markers, such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-6, and IL-1, which increases insulin resistance and alters the system. [25-28]

Hospital use of continuous glucose monitors (CGM). CGMs are currently FDA-approved in the outpatient setting to complement information obtained from standard self-monitored blood glucose (SMBG) testing and to aid in detecting hyper- and hypoglycemic episodes in patients with known DM.[29,30] CGMs provide an estimated capillary BG level through direct measurement

of interstitial glucose levels every 5-15 minutes. Several available CGM systems have achieved accuracy levels determined by mean absolute relative difference (MARD) values of <10% and no longer require confirmation testing or calibration with fingerstick glucose testing prior to making DM treatment decisions.[31-33] Few randomized controlled trials have been published on the safety and efficacy of CGM technology in the hospital.[34-37] In a recent study of hospitalized patients with DM, Gomez and Umpierrez reported increased detection of both hypo- and hyperglycemic events with the use of CGM compared to the standard of care POC BG testing in insulin treated patients with DM.[38] A recent panel of experts in inpatient diabetes care reported that CGMs are more effectively identifying trends toward hypoglycemia and hyperglycemia that may allow for better and safer management of patients with hyperglycemia, including those with SH.[37] More recently, several studies have reported on the meaningful use of CGM technology in the inpatient setting, assessing glycemic control outcomes using time within target glucose range in patients with DM.[39,40]

Our previous data indicates that SH is most likely to develop within the first 24-48 hours postoperatively (Figure 4); however, the precise onset and duration of SH remains unknown given the intermittent nature of POC BG testing. The use of CGMs to study SH will address this important gap in knowledge and determine the actual onset, duration, and severity of SH while providing information on glycemic control patterns in the perioperative period.

Effects of GLP-1 RA and pharmacokinetics of dulaglutide. GLP-1 is an incretin hormone secreted in the gut in response to meal ingestion, targeting multiple tissues throughout the body. One of its main targets is the pancreatic β-cell, resulting in increased insulin secretion and inhibition of glucagon production.[41] Additionally, GLP-1 has been shown to delay gastric emptying and promote satiety and weight loss through its direct effect on the autonomic nervous system, as well as through a centrally-mediated decrease in appetite via the hypothalamus.[42-44] Previous studies have shown cardiovascular (CV) benefits[45,46] mediated through both effects on CV risk factors (weight loss, reduction in blood pressure, improved lipid metabolism), as well as direct effects on the vascular endothelium (vasodilation, decreased inflammation).[46,47] Dulaglutide is a fusion protein of a GLP-1 analogue and a modified IgG Fc fragment, leading to a longer acting, relatively flat insulinotropic profile with increased plasma half-life suitable for once-weekly administration.[48] Previous trials have demonstrated improved glycemic control with both available doses of dulaglutide (0.75 mg and 1.5 mg administered once-weekly) when compared to other antihyperglycemic agents.[49-51] Phase 1 pharmacodynamic analysis in non-diabetic participants demonstrated median maximum plasma concentrations of dulaglutide between 24-48 hours after single-dose administration.[52]

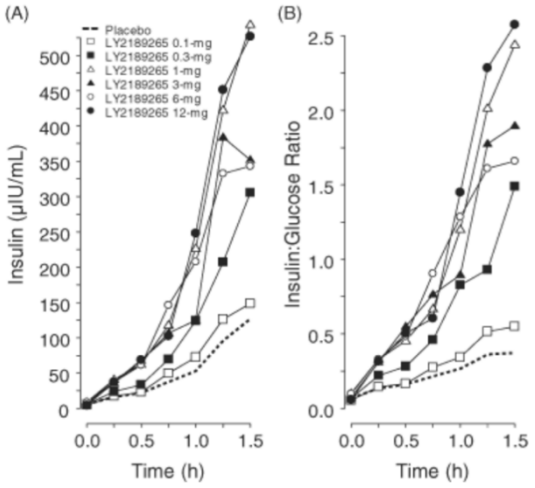


Figure 1. From: Barrington et al. Diabetes Obes Metab. 2011 May;13(5):434-8. "Figure 2. Insulin levels (A) and the ratio of insulin to glucose (B) were plotted vs. time following stepped glucose infusion in healthy subjects."

Further evaluation with stepped glucose infusion 3 days after dulaglutide administration revealed a dose-dependent rise in insulin secretion (Figure 3) and associated decline in serum glucose concentration.[52] Similar to other GLP1-RA, the most frequent adverse effects with dulaglutide were gastrointestinal and dose-dependent, with lower rates compared to short-acting GLP-1 RA.[52,53] The above data suggest that a single subcutaneous dose of 0.75 mg of dulaglutide will increase glucose-dependent insulin secretion and decrease glycemic excursions which may prove effective in preventing the development of stress hyperglycemia.

Glycemic control profiles and underlying dysglycemia risk. Over the past several years, there has been a growing interest in understanding CGM data in populations without diagnosed diabetes. With the amount of glucose data obtained by CGM, there is an opportunity to detect early patterns of dysglycemia that may not be captured by more traditional methods (e.g., OGTT, HbA1c).[54-57] Recent studies have demonstrated the potential predictive value of CGM to detect patterns of glucose dysregulation associated with pre-diabetes, diabetes and cardiovascular risk.[58-60] Similarly, emerging data from studies in pregnant women has suggested that early CGM patterns are useful in predicting the development of gestational diabetes and neonatal outcomes.[61,62]
In the perioperative period, interest in CGM has mainly surrounded use of real-time glucose monitoring for people with diabetes. To our knowledge, there is no current data on how CGM may be used to determine perioperative dysglycemia risk in patients without diabetes. Furthermore, there is no data on the duration of preoperative CGM wear needed to detect meaningful patterns of glucose dysregulation associated with SH. Preoperative assessments of dysglycemia have historically relied heavily on HbA1c testing, though there is concern that this metric may fall short in detecting dysglycemia particularly among some racial ethnic minority populations.[63,64] However, performing more comprehensive preoperative analyses, including OGTT, raises questions of feasibility and practicality for patients and providers within the current preoperative care model. Understanding the predictive value of shorter duration preoperative CGM wear for anticipating development of SH presents an opportunity to change the paradigm of preoperative screening practices.

4. Study Endpoints

Primary outcome (Aim 1):

- Incidence of SH in a population at high-risk for perioperative dysglycemia

Secondary outcomes (Aim 1):

- Differences in baseline insulin secretion and sensitivity between patients with and without SH.
- Differences in pre- and postoperative inflammatory and oxidative biomarker levels between patients with and without SH.
- Average onset and duration of SH by CGM (glucose >140 mg/dL) during the postoperative period.
- Mean and maximum daily glucose values (as measured by both POC glucose testing and CGM data).
- Identification of phenotypes and demographics associated with the development of SH.

- Differences in clinical endpoints between patients with and without SH, including: total daily insulin dose, length of hospital stay, ICU transfer, hospital readmission and emergency room visit after discharge
- Individual and composite of complications, including: wound infection, respiratory failure, pneumonia, acute kidney injury (increase in creatinine by 0.5 mg/dL), and major adverse cardiac events (MACE).

Primary outcome (Aim 2):

- Time in target glucose range (70-140 mg/dL) as determined by CGM during the postoperative period in high-risk patients undergoing major general and vascular surgery.

Secondary outcomes (Aim 2):

- Time-in-hyperglycemia (>140 mg/dL and >180 mg/dL).
- Percentage of time in hypoglycemia (glucose <70 mg/dL, <54 mg/dL, and <40 mg/dL) by CGM.
- Glycemic variability (as determined by coefficient of variation and standard deviation).
- Average onset and duration of SH during the postoperative period by CGM data.
- Mean and maximum daily glucose values (as measured by both POC glucose testing and CGM).
- Perioperative insulin requirements (total daily insulin dose).
- Differences in postoperative inflammatory and oxidative stress biomarker levels.

Primary outcome (Updated Aim 2):

- Characterization of glycemic control profiles (groups) indicative of SH risk.

Secondary outcomes (Updated Aim 2):

- Preoperative CGM metrics (time in ranges [TIR, TAR, TBR], %CV, MAGE) associated with SH.
- Minimum preoperative CGM data necessary for determination of pattern association with SH.
- Concordance of high-risk CGM profiles with established measures of dysglycemia (OGTT, HbA1c).

5. Study Intervention/Investigational Agent

Both aims of this study will employ the use of a blinded CGM (Abbott FreeStyle Libre Pro, FDA-approved) that will capture continuous glucose data. This data will not be visible to providers or used for clinical care. The device will be handled and managed by the study team only. The CGM sensor will be placed at the preoperative study visit in the CRC by an approved study team member.

The interventional aim [Aim 2, DISCONTINUED] of this study involved the administration of dulaglutide, a once weekly injectable GLP-1 RA approved for the treatment of type 2 diabetes, within 72 hours prior to surgery to determine if single dose administration of this agent can prevent the development of stress hyperglycemia. There is an IND exemption for dulaglutide for this study. The dulaglutide was handled by the Emory and Grady research pharmacies. Administration of dulaglutide occurred preoperatively at the CRC and was administered by a CRC nurse (study team blinded).

The standard of care for management of hyperglycemia in the hospital is insulin therapy. During hospital admission, should any participant develop elevated blood glucose values, they will receive standard-of-care insulin therapy as per hospital protocol (outlined below in *Research Procedures* section).

6. Procedures Involved

A total of 245 patients were planned for enrollment in order to have 80 patients from this group randomized to participate in Aim 2 (Figure 4). This number has been updated to a planned enrollment of 165 patients (Aim 1 and Updated Aim 2) since the discontinuation of the clinical trial aim (Aim 2).

Patients will be consented and randomized at their CRC visit for OGTT and CGM placement. Participants will undergo a 2-hour 75g OGTT with blood samples measured at 6 timepoints during the 2 hour timeframe (at 0, 15, 30, 60, 90, 120 minutes).

Those with OGTT or HbA1c results revealing presence of pre-DM or newly diagnosed DM were previously asked to participate in Aim 2. Patients consenting to participation received a single subcutaneous injection of dulaglutide or saline placebo (within 72 hours prior to planned surgical intervention). Both study team and patient were blinded to randomization with the assistance of the Research Pharmacist and CRC nurse.

Preoperative glycemic control and inflammatory/oxidative stress biomarkers will be collected as described in Aim 1. Inpatient glycemic control parameters will be followed with POC glucose testing (standard-of-care) and blinded CGM.

Prior to admission:

- Patients will be invited to participate prior to or at their preoperative clinic visit. Informed consent will be obtained by designated study personnel.
- Within 72 hours preoperatively:
  Aim 1, Aim 2, Updated Aim 2
  - Oral glucose tolerance testing (OGTT) to assess insulin secretion and action, and for the presence of dysglycemia or diabetes.
  - Placement of blinded CGM sensor (Abbot FreeStyle Libre Pro).
  - Collection of blood samples for inflammatory/oxidative stress biomarkers and hemoglobin A1c.

  Aim 2 only [DISCONTINUED]

  - Subcutaneous injection of dulaglutide or saline placebo.
- Patients are liable to have surgery dates rescheduled for varying reasons after the study preoperative clinic visit. In the event that patients have their surgery dates changed after the preoperative clinic visit to a later date that falls out of the window period of 72 hours before surgery, the patient will only be retained to complete the study if the new date is within 3 months from the day of the study preoperative clinic visit. This category of patients will have their blinded CGM sensor retarted within 72hours of the new surgery date but the OGTT procedure will not be repeated. However,if the new surgery date falls outside a duration of 3 months from the study preoperative clinic visit, the patient will be excluded

from the study as a screen failure. They may choose to participate in the study, but will be consented again and undergo full study procedures.

During hospital admission:

- Standard-of-care POC capillary BG will be measured prior to surgery, hourly during surgery and in the recovery room. After the patient is transferred to regular floor, POC BG testing will be performed as per hospital protocol.
- Patients who develop SH postoperatively will be treated with insulin as per institution protocol (standard of care, outlined below).
- The CGM sensor placed before surgery will be continued during the hospital stay (up to 14 days in total, life of sensor).

Inflammatory and oxidative stress biomarkers will be measured at 48-72 hours postoperatively.

Initiation of "rescue therapy" with subcutaneous insulin. Patients with fasting and/or premeal BG >180 mg/dl will receive coverage with sliding scale insulin (supplements). Those with 2 consecutive fasting and/or premeal BG >180 mg/dl or with average daily BG >180 mg/dl, will be started on basal (detemir or glargine) insulin once daily as per Emory protocols (see below).

Supplemental (correction) insulin. Supplemental (lispro or aspart) insulin will be administered following standard "sliding scale" protocol outlined below.
Supplemental Sliding Scale Insulin (number of units) - administer dose before meals.

Blood Glucose (mg/dl)	☐ Sensitive	☐ Usual	☐ Resistant
181-220	2	3	4
221-260	3	4	5
261-300	4	5	6
301-350	5	6	7
351-400	6	7	8
> 400	7	8	9

** Check appropriate column below and cross out other columns

At bedtime, give according to Bedtime Supplemental Sliding Scale Insulin starting at BG >220 mg/dl:

Blood Glucose (mg/dl)	☐ Sensitive	☐ Usual	☐ Resistant
221-260	1	2	3
261-300	2	3	4
301-350	3	4	5
351-400	4	5	6
> 400	5	6	7

** Check appropriate column below and cross out other columns

The numbers in each column indicate the number of units of aspart or lispro insulin per dose. If a patient is able and expected to eat all or most of his/her meals, supplemental insulin will be administered before each meal following the "usual" column dose. Supplemental insulin at bedtime = half of premeal insulin dose at BG > 220 mg/dl. If a patient is not able to eat (NPO), supplemental insulin will be administered every 6 hours (6-12-6-12) following the "sensitive" column dose.

Basal insulin therapy with Detemir or Glargine:

- Patients with average BG between >180 mg/dl= start detemir or glargine at 0.2 units per kg weight per day.
- Patients with GFR <50 or over the age of 70= start detemir or glargine at 0.1 units per kg weight per day.
- Basal insulin will be given once daily, at the same time of day.

Insulin adjustment. The total detemir or glargine daily insulin dose will be adjusted as follows:

- Fasting and pre-meal BG between 100-180 mg/dl without hypoglycemia the previous day: no change
- Fasting and pre-meal BG between >180-240 mg/dl: increase detemir or glargine dose by 10% every day
- Fasting and pre-meal BG >241 mg/dl: increase detemir or glargine dose by 20% every day
- Fasting and pre-meal BG <100 mg/dl: reduce detemir or glargine by 20% or stop if patient is already on less than 0.1 units/kg of body weight

7. Data and Specimen Banking

The study coordinator and/or investigator will enter baseline and daily data into data collection paper forms and an electronic database provided by the Emory Research Information Technology Department (REDCap). Baseline data will include demographics/history form (subject gender, date of birth, ethnicity, dates of hospitalization and operation, comorbid conditions, body weight, BMI, and type of surgery). Daily information will be collected on treatment (insulin dosage, antibiotics), nutrition support, BG and laboratory values, hospital complications and adverse events, and length of ICU and hospital stay.

Participants in both aims of the study will have their blood samples and data stored for future research and use by Dr. Davis and designated study team for further investigation into the mechanisms of stress hyperglycemia and other aspects of glycemic control. Samples will be stored in a secured freezer in the study team's designated lab with restricted access indefinitely.

8. Sharing of Results with Participants

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

- This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers up to 12 months after the completion of the primary endpoint by contacting the Principal Investigator.

- Dr. Davis will ensure proper registration of the clinical trial and that results are submitted to "Clinicaltrials.gov", per Emory internal policy and as stated in the program. Data obtained from the observational study (Aim 1, Updated Aim 2) and clinical trial (Aim 2) will be presented at national and local meetings, in a de-identified format. All final peer-reviewed publications will be placed in the digital archive in PubMed Central.

9. Study Timelines

The duration of active study participation for each individual participant will be up to a maximum of 14 days, depending on their length of surgical hospitalization. We anticipate completion of enrollment for all Aims (Aim 1, Aim 2, Updated Aim 2) over a total of 5 years.

10. Inclusion and Exclusion Criteria

Inclusion criteria (Aim 1, Updated Aim 2):

- Men and women between the ages of 45 and 80 years undergoing non-cardiac general or vascular surgery
- BMI ≥28 kg/m^2 without a previously known history of DM

Exclusion criteria (Aim 1, Updated Aim 2):

- Patients prescribed or taking antihyperglycemic medications
- Patients undergoing cardiac surgery or patients anticipated to require ICU care
- Patients with Hemoglobin <10 gm/dL
- Patients expected to be admitted less than 48-72 hours after surgery
- Severely impaired renal function (eGFR < 30 mL/min) or clinically significant hepatic failure
- Treatment with oral (equivalent to prednisone > 5 mg/day) or injectable corticosteroids
- Mental condition rendering the subject unable to understand the nature, scope, and possible consequences of the study; unable to consent
- Pregnant or breast-feeding at time of enrollment
- Prisoners

Inclusion criteria (Aim 2) [DISCONTINUED]:

- Men and women without known history of diabetes with ages between 45 and 80 years undergoing non-cardiac general or vascular surgery participating in Aim 1.

- BMI ≥28 kg/m2 and pre-DM or DM by OGTT or HbA1c.

Exclusion criteria (Aim 2) [DISCONTINUED]:

- Same as in Aim 1, with the following additional exclusion criteria:
- Patients undergoing gastrointestinal surgery or at high risk for gastrointestinal obstruction/ileus or expected to require gastrointestinal suction
- Patients with delayed gastric emptying, pancreatic or gallbladder disease
- Patients with personal or family history of medullary thyroid cancer or multiple endocrine neoplasia syndrome type 2 (MEN2)

11. Local Number of Participants

We plan to recruit a total of 165 patients for this prospective study, enrolling at least 100 patients with adequate CGM data for analysis in Updated Aim 2. No further enrollment will occur for the clinical trial (Aim 2).

12. Recruitment Methods

All proposed aims will take place at Grady Memorial Hospital and Emory University Hospital. There will be no other collaborating sites. All patients scheduled to undergo general or vascular surgery will be considered potential candidates in this study. We will also recruit study participants scheduled for perioperative appointments via the Emory Telehealth services.

A partial HIPAA waiver will be obtained to review electronic health records, scheduling logs and inpatient admission rosters to identify potential study participants undergoing perioperative evaluation. Patients will be approached and informed of this study by a member of the study team or their treating surgical team prior to (by telephone) or during their preoperative clinic evaluation prior to scheduled surgery. Potential participants interested in study participation will be invited over and consented at an in-person visit (CRC) before administering study procedures.

13. Withdrawal of Participants

- If a subject becomes incarcerated during the study, develops a serious medical or psychiatric illness during the study, they will be disqualified from participating further in the study. If a participant wishes to discontinue participating in the study, they will be able to withdraw at any time by informing the study team. Study data collected up until participant withdrawal will remain part of the data for this study. This information continues under the Certificate of Confidentiality. Patients who have their surgery rescheduled to a later date that falls outside a duration of 3 months from the study preoperative clinic visit will be excluded from the study as a screen failure.

14. Risks to Participants

Risks associated with use of dulaglutide: Dulaglutide is a widely used antidiabetic agent with a proven safety profile. The major adverse events most frequently reported with dulaglutide 0.75 mg weekly dosing are mainly gastrointestinal; nausea (12.4%), vomiting (6%), and diarrhea (8.9%), abdominal pain (6.5%), decreased appetite (4.9%), dyspepsia (4.1%), and fatigue (4.2%). In most cases nausea is mild and transient with less than 5-10% discontinuation of the drug due to side effects. In our preliminary studies with daily administration of the short-acting exenatide, less than 10% of patients developed nausea and none out of over 100 patients in our pilot study discontinued the drug due to GI side effects. Dulaglutide, like other GLP-1 RA, is a rare cause of pancreatitis.

New information regarding the risk of GLP-1 RA use in the perioperative period includes concern for an increased risk of gastric aspiration during anesthesia procedures. For this reason, Aim 2 has been discontinued.

Risk of hyperglycemia and hypoglycemia: Patients with perioperative hyperglycemia remain at risk for increased rates of complications, and those developing blood glucose levels >180 mg/dl will receive insulin therapy. The risk of hypoglycemia with the use of dulaglutide is low, nearly comparable to placebo. There is an increase in hypoglycemia risk with the use of insulin. The number of mild and severe hypoglycemic episodes and clinical consequences (neurological and cardiovascular) will be analyzed.

Risk of oral glucose tolerance testing (OGTT): The oral glucose solution used for the 75g OGTT carries minimal risk and is used commonly to diagnose diabetes. Potential rare adverse reactions: nausea, vomiting, abdominal bloating, and headache. In addition, there is a rare incidence of hypoglycemia.

Risk of continuous glucose monitor (CGM) use: No major risks are anticipated with the use of the CGM device. Pain and bleeding with insertion is minimal. Skin irritation may occur in relation to the adhesives. Other potential risks of using CGM described in the literature include unrealistic glycemic control expectations, and effects of continued alerts and alarms; these potential drawbacks will not be associated with the use of the FreeStyle Libre Pro CGM given results will be blinded to patients and nursing staff.

Treatment of hypoglycemia: Hypoglycemia, defined as a BG <70 mg/dl will be treated by a standard hypoglycemia protocol available at the institution.

Phlebotomy: Risks associated with phlebotomy and IV insertion are low and include small amounts of pain, possible bruising, swelling, redness, and rarely an infection at the site or fainting. A total of ~60 ml of blood will be obtained during the pre- and postoperative lab collections.

15. Potential Benefits to Participants

Potential Benefit: Patients with stress hyperglycemia experience more complications and higher rates of mortality. For Aim 1 and Updated Aim 2, There is no direct benefit to the study subject

for participation in this prospective observational trial. However, the study may increase the subjects' awareness and identify early abnormalities in glucose metabolism.

For Aim 2 [DISCONTINUED], there is a potential for direct benefit to the study subject for participating in the study should dulaglutide be effective in the prevention of stress hyperglycemia.

Risk of anticipated benefit: The overall risk associated with the observational aims (Aim 1 and Updated Aim 2) of this study is low.

We have discontinued Aim 2 that involves the administration of dulaglutide due to the potential risk of gastric aspiration during anesthesia. We will take extensive precautions to reduce risks associated with CGM use and phlebotomy and ensure that subjects' data remains confidential. Although the subject may or may not benefit directly from this study, this study can yield important information regarding patients who may be at risk of developing perioperative hyperglycemia, leading to poor clinical outcomes. Therefore, the risk to benefit ratio favors conducting Aim1 and Updated Aim 2 of this study.

16. Compensation to Participants

Study participants will be given an incentive for the time and effort required to be a part of this study. For study Aims 1 and Updated Aim 2, 165 participants will undergo oral glucose tolerance testing (OGTT) at the Clinical Research Center and will wear a CGM during surgical admission. They will receive compensation of ($50) at completion of their CRC study visit and an additional $25 at hospital discharge.

Those participants enrolled previously in Aim 2 [DISCONTINUED] and completing a preoperative OGTT, CGM sensor wear and dulaglutide or placebo injection received ($50) at completion of their CRC study visit and were compensated an additional $50 at the time of hospital discharge.

17. Data Management and Confidentiality

Statistical Analysis Plan:

Assessment of baseline clinical characteristics. Preoperative information regarding demographics, anthropometrics, medical, family and social histories will be obtained through direct patient interview and review of the electronic medical records.

Assessment of insulin secretion and action during OGTT. Plasma glucose and insulin response during a 75g OGTT reflect the ability of pancreatic β-cells to secrete insulin, as well as the sensitivity of tissues to insulin action.[65-71] We propose using a battery of indices calculated from the OGTT to assess insulin dynamics including: **a) insulin secretion capacity from pancreatic β-cell** by measurement of fasting insulin (FI), calculation of the Insulinogenic Index[72] and the Corrected Insulin Response at 30 minutes (CIR_{30})[73] **b) whole body insulin sensitivity** through use of the reciprocal of the Homeostasis Model Assessment of insulin resistance (1/HOMA),[70] Quantitative Insulin Sensitivity Check Index (QUICKI)[65,70,71] and the Composite Insulin Sensitivity Index (CISI).[74] During the OGTT, blood samples will be obtained at six timepoints: 0, 15, 30, 60,

90, and 120 minutes. OGTT will be performed at Emory University and Grady Hospital Clinical Research Centers.

Formulas of Insulin Secretion:
CIR$_{30}$ = I_{30} x 100 / [G_{30} x (G_{30} - 70)] (I_{30} = Insulin at 30 minutes, G_{30} = glucose at 30 minutes)
Insulinogenic Index = $\frac{I_{30} - FI\ \mu U/mL}{G_{30} - FBG_{\ mg/dL}}$
Formulas for Whole Body Insulin Sensitivity:
CISI = $\frac{10000}{\text{Square Root [(FI x FBG) x (mean insulin (0-120 min) x mean glucose (0-120 min)}}$
QUICKI = (I/log FI µU/mL) + log FBG

Assessment of inflammatory and oxidative stress markers. Serum inflammatory and oxidative stress markers measured preoperatively and 48-72 hours postoperatively will include: plasma cortisol, free fatty acids (FFA), high sensitivity C-reactive protein (hsCRP), tumor necrosis factor-alpha (TNF-α), adiponectin, and thiobarbituric acid reactive substances (TBARS).

Assessment of perioperative glycemic control by CGM. Glycemic control will be assessed by POC testing (standard-of-care) and blinded CGM. Placing the Abbott FreeStyle Libre Pro CGM sensor preoperatively will allow for stabilization and calibration of estimated glucose levels prior to surgical intervention. Patients will wear the CGM sensor during surgical hospitalization, up to 14 days in total (lifetime of CGM sensor). The study team, patients and nursing staff will remain blinded to CGM values, continuing to provide standard-of-care blood glucose monitoring through POC testing.

Aim 1a: We will obtain information on patient demographics, as well as glucose and insulin levels during OGTT to estimate insulin sensitivity and β-cell function. The primary outcome for Aim 1a is the binary outcome indicating whether or not SH has occurred.

We will first summarize collected clinical characteristics and metabolic and inflammatory biomarkers over all subjects and by the status of SH occurrence, using standard summary statistics, such as mean+/- standard deviation (SD), median and (interquartile) range, count and relative frequency. Next, we will assess the marginal association of each of the potential SH predictors with the occurrence of SH. To this end, we will apply t-tests or nonparametric Wilcoxon tests when the potential predictor is continuous and apply Chi-square or Fisher's exact tests when the potential predictor is discrete. Following the marginal association analyses, we will build multivariate models for the occurrence of SH based on logistic regression models to develop a risk prediction tool. To select variables included in the final predictive model, we will consider three strategies: (i) using classic forward or backward model selection procedures based on criterion such as Akaike information criterion (AIC) or Bayesian information criterion (BIC); (ii) employing regularized logistic regression based on Lasso,

adaptive Lasso, or elastic-net penalty to simultaneously achieve variable selection and shrinkage estimation; iii) utilizing the random forest technique to provide intuitive illustrations of the importance of each potential predictor and obtain simple decision rules for predicting the occurrence of SH. We will evaluate and compare the SH prediction rules derived from the approaches described above using accuracy measures, such as Yoden's index for receiver operating characteristic (ROC) and different types of C-statistics. The assessment of these accuracy measures may be conducted via K-fold cross validations.

Aim 1b: We will summarize various temporal features of glucose patterns during the hospital stay (e.g. duration of SH, glycemic variability) using CGM data. The primary outcome for Aim 1b is the percentage of time with glucose >140 mg/dL, as determined by CGM data.

Similar to the analysis plan for Aim 1a, we will first calculate summary statistics, followed by marginal association analysis between the percentage of time with glucose >140 mg/dL and each potential risk factor. Then we will conduct multivariate analyses based on linear regression. We will perform variable selection following the first two strategies outlined for Aim 1a. We will assess the multivariate models based on predictive measures such as apparent error or absolute prediction error, possibly obtained from cross-validation. For the secondary outcome regarding the timing of SH, we will consider formal survival analysis to summarize its distribution by Kaplan-Meier curves and perform univariate and multivariate analyses based on Cox regression models or censored quantile regression models.

Aim 1c: The primary outcome for Aim 1c is the binary outcome indicating the occurrence of any perioperative complications. We will compare the duration and severity of SH between the patient groups with and without any perioperative complications based on t-tests or Wilcoxon-tests. Further multivariate analyses will be conducted similarly to those described for Aim 1a.

Aim 2 [DISCONTINUED]: The primary outcome of Aim 2 is the proportion of time in target glucose range (70-140 mg/dL) by CGM. We will use nonparametric Wilcoxon tests for comparisons between the two treatment groups, followed by multivariate linear regressions that adjust for potential confounders, such as age and gender. For discrete secondary outcomes, we will use two-sided Chi-square tests or Fisher's exact test to compare the primary outcome between the dulaglutide treatment group and the placebo group. We will also perform multivariate logistic or Poisson regression to estimate the difference between the two treatment groups while adjusting for other relevant covariates. To build an adequate multivariate linear or logistic regression model, we will adopt standard stepwise, backward, or forward model selection strategies. Standard diagnostic and model checking procedures, such as residual/leverage plots, deviance residual plot and Hosmer-Lemeshow test, will be applied to examine the fit of the final linear or logistic regression models.

The planned statistical analysis for this discontinued Aim 2 will be exploratory and include all patients enrolled prior to discontinuation.

Updated Aim 2:

Assessment of CGM data adequacy. Based on preliminary estimates, adequate CGM data for analysis will be defined by more than12 hours of preoperative and over 24 hours of postoperative sensor wear with at least 70% sensor glucose data acquisition. The first 6 hours

of wear will be excluded to ensure sensor reading stability and to exclude glucose changes related to OGTT testing.

Assessment of preoperative glycemic control by CGM. Preoperative CGM data will be assessed using established glycemic control metrics including: time in range (TIR, 70-140 mg/dL), time above range (TAR, >140 mg/dL, >180 mg/dL), time below range (TBR, <70 mg/dL, <54 mg/dL), percent coefficient of variation (%CV), mean amplitude of glycemic excursions (MAGE) to determine the association of these indices with the development of SH postoperatively.

Identification of high-risk preoperative glycemic control profiles by CGM. Clustering analysis techniques will be used to identify unique patterns of glycemic control associated with postoperative SH and define groups or participants at high risk for SH based independently on preoperative CGM data.

Comparison of CGM profiles with established metrics of dysglycemia. CGM profiles associated with varying SH risk will be compared to metrics of dysglycemia obtained in Aim 1 (OGTT, HbA1c) to assess for concordance.

Sample Size and Power Calculation:

We plan to recruit 165 patients for Aim 1, obtaining 100 patients with adequate CGM data for Updated Aim 2. Based on preliminary data in over 7,000 high-risk surgical patients (age >45 years and/or BMI >25 kg/m^2) at our institution without a known history of DM, preoperative HbA1c testing revealed normoglycemia (<5.7%) in 69%, pre-DM (5.7-6.4%) in 27.2% and newly-diagnosed DM (≥6.5%) in 3.9% of patients.[75] We anticipate higher rates of pre-DM and DM in our population with higher BMI (≥28 kg/m^2) and the use of IFG and IGT criteria in addition to HbA1c for improved detection of underlying dysglycemia.

Our preliminary data from retrospective chart review showed that 38% of non-DM patients with age >45 years and BMI ≥28 kg/m^2 developed SH following general surgery by POC testing. With CGM, we anticipate a higher rate of SH detection, and assume 50% of high-risk subjects with underlying dysglycemia will develop SH. Our power calculations are performed conservatively based on multiple univariate comparisons of potential predictors, such as β-cell function, insulin sensitivity and inflammatory/oxidative biomarkers between patients with SH and without SH. A final sample size of 205 will provide 80% power to detect a mean difference in potential predictor equal to 0.66 times the corresponding SD, based on two-sample, two-sided t-tests with FDR controlled under 20%.

For Updated Aim 2, we anticipate sufficient pre-op and post-op CGM data from 100 patients. Considering 10 CGM features and assuming 50% rate of SH, with the sample size of 100, we would have 80% power to detect the effect of a CGM feature with the effect size (i.e. mean difference) equal to 0.75 times the corresponding SD, based on two-sample, two-sided t-tests and Bonferroni correction. Regarding the clustering analyses, aiming for at least 20-30 patients per subgroup (or cluster), the sample size of 100 would be reasonable to identify three well-separated clusters.[64]

We will compare our research endpoints between male and female subjects and will include sex as a covariate when building our predictive models.

Data Management and Confidentiality:

Data to be collected: Demographic information, physical exam findings during hospitalization such as blood pressure, weight etc.., checklist of inclusion/exclusion criteria, lab and glycemic control data will be collected.

Access to identifiable private information: Only study investigators and staff will have access to individually identifiable private information of the study subjects. The unique study subject charts will be kept in a locked cabinet in the study team's research office. An access card and badge are needed to enter the research office.

All subjects will be assigned a unique study identification number. The study ID numbers linking to the identifiable information will be kept in a locked cabinet. All samples collected from this study will be stored using the unique study ID number. Information needed for this study will be collected by the PI and the study coordinator. All the study team members will have completed and documented the appropriate human subjects training. The nursing staff will perform the phlebotomy. Only approved study team members and CRC staff will have access to the specimens. Data and specimens will be stored indefinitely using study ID numbers in a secured freezer within the CRC or designated research team lab with restricted access to approved personnel. If specimen transport is required for certain testing, all shipment procedures will be handled in concordance with institution and lab safety and processing requirements by a member of the study team.

This research is covered by a Certificate of Confidentiality from the National Institutes of Health.

18. Provisions to Monitor the Data to Ensure the Safety of Participants

The Data and Safety Monitoring Plan (DSMP) will include 4 independent reviewers [Data Safety Monitoring Board (DSMB)] to monitor safety, treatment compliance, and clinical procedures in this observational study (Aim 1 and Updated Aim 2). The DSMB will meet at 6-month intervals and report on study progress to the IRB.

Interim Analysis and Stopping Rules: Safety monitoring analysis will be performed every 3 months or when half of the subjects are randomized. The trial will be stopped at the discretion of the DSMB if there is concerning evidence of a difference in the rate of death and/or hospital complications (two-sided alpha level, <0.01) between the treatment groups.

Should the rate of mild hypoglycemia (BG <70 mg/dL) exceed 40%, or the rate of severe hypoglycemia (BG <40 mg/dL) exceed 20% in the treatment group, the trial will be stopped.

The DSMP outlined below will adhere to the protocol approved by the CRN Scientific Advisory Committee and the Emory University IRB. An IRB-approved written informed consent will be obtained from each subject at entry into the study; elements of informed consent will include: (a) having the subject and/or guardian/proxy review the study consent form; (b) having the investigator(s) or study staff meet with the subject and/or guardian/proxy to review the

consent, confirm understanding, and answer any questions; and (c) once the investigator(s) or study staff are convinced that the protocol is understood and that there is agreement to participate, having the consent signed.

Research meetings will be held regularly (at least monthly during the first three months of study initiation and bimonthly from then on) where study progress will be discussed to include enrollment numbers, any unanticipated issues with protocol logistics or adherence, adverse events, potential risks, need for protocol modifications, compliance with Clinical Trial Protocol requirements and any emergent problems. Those not attending the meeting will be updated via email regarding the matters discussed during the meeting.

The PI and other study team members will review all data collection forms for completeness and accuracy of the data as well as protocol compliance. The PI will review this protocol on a continuing basis for subject safety and include the results of the review in annual progress reports submitted to the DSMB. The results of the review will also be included in annual progress reports submitted to the local institutional IRB, as required.

Patient Monitoring: will be performed by the PI, Co-Investigators, and Research Coordinator(s). Patient safety data examination, monitoring procedures/oversight:

- All adverse events (AEs) will be graded as to their attribution (unrelated to protocol, or possibly, probably, or definitely related to protocol).
- Any AE that is reported to either the site investigator or designated research associates by a study subject or medical staff will be documented as per IRB protocol.
- This study will be entered into the Emory REDCap computerized database system to permit tracking of adverse events.
    - This system will then be used by all investigators to report “expected” AEs (predefined AEs which will be monitored over the course of the trial – see below), “observed” AEs (AEs which occur but which may or may not have been anticipated), and all serious adverse events (SAEs).
    - Serious adverse events are predefined as: any experience that suggests a significant hazard, such as events which: a) are fatal, b) are life threatening, c) result in permanent disability, d) require inpatient hospitalization, or e) involve cancer, a congenital anomaly, or drug overdose.

The standard Emory IRB reporting guidelines for AE and SAE reporting will be followed. The site investigators and staff will enter all AEs into the Emory REDCap database, and evaluate the SAEs. The investigators and staff will track and summarize AE frequency, severity, and relatedness at a frequency appropriate to ensure subject safety.

A periodic (annual unless otherwise specified) report of AEs with a frequency > 5% will be provided to the DSMB for this clinical trial 1-2 months prior to IRB annual review. The Emory IRB reporting guidelines for UP, AE and SAE reporting will be followed.

19. Provisions to Protect the Privacy Interests of Participants

This research is covered by a Certificate of Confidentiality from the National Institutes of Health, which limits identifiable information from being shared with other parties.

Participants will be informed of all planned procedures during the informed consent process and will have the opportunity to ask questions at any time to members of the study team during their participation. Should they not wish to continue with study procedures, they may withdraw from participation at any time.

Patients enrolled in the study will receive standard of care treatment for any hyperglycemia that develops postoperatively. Insulin treatment for stress hyperglycemia is standard of care and all subjects in this study will receive this if needed. This will be made clear before any subject signs the informed consent. If subjects do not want to participate in the study, they will be assured that they will receive care that they are otherwise entitled to without bias.

20. Economic Burden to Participants

Patients will be responsible for costs associated with attending the preoperative study visit at the CRC. They will be compensated for their time and participation as previously described. Patients will be responsible for the costs of their planned surgical hospitalization but will not be charged for study-related labs.

21. Informed consent and randomization

All patients scheduled to undergo surgery will be considered potential candidates in this study. Patients will be invited to participate during or prior to their preoperative clinic evaluation at least 72 hours prior to scheduled surgery. The investigators or study coordinators will review and explain the contents of the informed consent document to the eligible patient. The potential subject will be informed of the purpose of the study, the randomization procedure, and the risks and benefits of participation. The potential subject will also be informed that he/she may refuse to participate, and that even if he/she consents to participate he/she may withdraw from the study at any time.

Prior to inclusion, individuals meeting inclusion/exclusion criteria will be provided basic information regarding the study. If interested, the consent form, potential risks and benefits, and the rights of research participants will be explained. Patients will be given ample time to review the consent form and ask questions about participation in the study. The consent form will be in accordance with the IRB and HIPAA guidelines of Emory University. Eligible and interested individuals will then begin the study after signing informed consent. The person obtaining consent will ensure participant understanding by assessing participant knowledge of the study procedures and potential risks. Participants will be assured that if they do not want to participate in the study, they will receive care that they are otherwise entitled to without bias. A signed copy of the consent form will be provided to the participant and a copy will be placed in a file that will be maintained for each participant in a locked cabinet in the study office.

Circumstances under which consent will be obtained: There will be no waiver of informed consent. If a potential subject has any psychiatric illness or a serious medical illness, he/she will

not be included in the study. All individuals that will be obtaining informed consent will have the appropriate training and certifications to perform human subjects' research. They will also be informed that this study will be for research purposes only and if they do not wish to participate, it does not preclude them from receiving usual medical care. They will also be informed of the right to withdraw from the study at any time and that their study information will be anonymous. Copies of the written consent will be given to all participants.

Non-English-Speaking Participants

The consent form for this study will be translated into Spanish. Spanish-speaking participants will go through the same consent process outlined above in the presence of an interpreter/interpretation service approved by the institution. Consent will be obtained by the same approved study personnel via interpretation services.

22. Setting

Participants who are scheduled for perioperative clinic evaluation will be recruited from the Grady Health System and Emory University Hospital. We will also recruit participants scheduled for perioperative evaluation via the Emory Telehealth services. Potential participants will be recruited prior to or during preoperative clinic visits within each hospital system. Research procedures preoperatively will take place at the Grady or Emory Clinical Research Centers, part of the Georgia CTSA.

23. Resources Available

Grady Memorial Hospital/Grady Health System: The Grady Health System is a large urban health care network located in Atlanta, Georgia. Grady operates under the Fulton-Dekalb Hospital Authority, helping to deliver care to their uninsured and underserved populations. The Grady Heath System includes separate adult and children's hospitals, as well as multiple hospital-based clinics throughout the Atlanta Metro area. The outpatient clinics provide care for more than 800,000 annual patient visits. Grady Memorial Hospital is a ~900-bed acute care facility located in downtown Atlanta, sustaining more than 45,000 admissions and performing ~7,000 inpatient and 3,000 outpatient surgeries annually. This will provide ample potential for recruitment of surgical patients to participate in this study.

Emory University Hospital: Emory University Hospital is a 587-bed tertiary care medical and surgical facility with over 24,000 admissions annually and performing ~10,000 inpatient and 3,000 outpatient surgeries in the most recent year reported. Emory University Hospital system is staffed by over 2100 faculty who are members of the Emory University School of Medicine, providing opportunities for interdisciplinary research endeavors. This environment will promote continued collaboration with surgical subspecialties and successful recruitment of surgical patients for this study.

Georgia Clinical &Translational Science Alliance and Clinical Research Network sites: *Georgia Clinical and Translational Science Alliance (Georgia CTSA):* The Georgia CTSA (georgiactsa.org), created in 2017 through a multi-institutional partnership between Emory University, Morehouse School of Medicine, University of Georgia and Georgia Institute of Technology, is one of 60 medical research institutions working as a national consortium funded by NIH/NCATS through the Clinical and Translational Science Awards (CTSA) program to improve clinical and

translational research nationally. A major goal of this program is to bring together basic, translational and clinical investigators, community clinicians, professional societies and industry collaborators in dynamic clinical and translational research projects. Included among priorities of the Georgia CTSA are to 1) create an Atlanta-wide translational science workforce to advance discoveries impacting human health, 2) encourage collaboration and community involvement to advance translational research, 3) create and provide new informatics solutions promoting best clinical practices and integrating clinical and basic data for translation to complex populations, and 4) integrate, improve and innovate the quality of education and training programs for the next generation of clinical and translational researchers. The Georgia CTSA includes units at Emory University Hospital, Children's Hospital of Atlanta at Egleston Hospital, Grady Memorial Hospital, and the Ponce HIV Center. Georgia CTSA resources include inpatient and outpatient units, research nurse support, Core Laboratory support and support from the Bionutrition Unit and Biostatistics and Informatics Unit.

The Grady CRC is located within Grady Memorial Hospital, 5C (5th floor) area and is part of the NIH-funded Georgia CTSA Clinical Research Network. The CRC area includes four outpatient care rooms, a nursing station, and a private room used for patient interviews. The inpatient portion has functional capacity for two research overnight beds, which will not be required for this proposal. The outpatient area consists of two beds and three infusion recliners, an outpatient nursing station and a rest room, which will be used for completion of the preoperative oral glucose tolerance tests and all phlebotomy procedures. There are administrative offices (medical director, nursing director, and a generic office for patient interviews shared by participating research staff). CRC nursing staff has extensive experience in conducting inpatient and outpatient clinical and metabolic studies, including performance of oral glucose tolerance testing required for this proposal. The Grady research laboratory occupies 1,824 square feet and is equipped with a specimen processing and aliquotting laboratory, -20°C and -80°C freezers, 4°C refrigerator, centrifuges, and molecular cell biology laboratory. As with the CRC at Emory University Hospital, all freezers/refrigerators are equipped with CO2 back-up system and web-based temperature monitoring system. The laboratory can collect, process and store blood assays generated by this research project. The Grady CRC is fully equipped, and the staff is well-trained to handle the procedures required by this research project.

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