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Title: Benefits of Insulin Supplementation for Correction of Hyperglycemia in Patients with Type 2 Diabetes Treated with Basal Bolus Insulin Regimen

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RESEARCH OBJECTIVES AND SPECIFIC AIMS

Several observational and randomized controlled trials (RCT) have reported that inpatient hyperglycemia is associated with an increased risk of complications and mortality (1-5). Several interventional trials have shown that treatment of hyperglycemia in critically ill and non-ICU patients is associated with shorter length of hospital stay and lower rates of hospital complications. Several prospective, randomized trials in general medicine and surgical patients with type 2 diabetes (T2DM) have shown that treatment with basal bolus insulin regimen results in better glycemic control and lower rate of hospital complications compared to treatment with sliding scale regular insulin in patients (4; 6-8). Indeed, basal bolus regimen is recommended in clinical guidelines by multiple professional societies (9; 10) for treatment of inpatient hyperglycemia and T2DM in non-ICU patients.

While basal bolus regimens are recommended, they consist of multiple daily injections. In addition, they require correction of blood glucose (BG) levels with supplemental (corrective) doses of insulin based on BG levels (4; 6; 7; 11; 12). Data from our group has shown that simplified regimens such as a basal-plus regimen may be just as effective for glycemic control as a basal bolus regimen (11). Additionally, recent data from one of our RCTs showed that corrective doses of insulin at bedtime for mild to moderate hyperglycemia, a standard of care practice, may not be necessary (13). Glycemic control, rates of hypoglycemia or total daily dose (TDD) of insulin did not differ whether corrective doses of insulin were given or not for bedtime hyperglycemia. Similar to this trial, several trials from our group with different basal bolus regimens show that the amount of supplemental insulin per day is between 5-9 units/day (See Table 1). It is possible that the use of insulin supplements may increase the risk of hypoglycemic events, an independent marker of mortality (14).These small amounts of daily supplemental insulin requirements raise the question of whether corrective doses of insulin before meals and bedtime are beneficial in inpatient treatment for T2DM.

Currently, no RCTs have prospectively evaluated the need for corrective doses of insulin as part of a basal bolus regimen in the inpatient setting. We propose to study the safety and efficacy of the standard practice of correcting mild to moderate hyperglycemia (BG 140-260 mg/dL) before meals and bedtime in patients treated with basal bolus insulin regimen. A glucose > 260 mg/dL was picked arbitrarily. **We hypothesize that correction of mild-moderate hyperglycemia with rapid-acting insulin analogs (standard of care) will not improve glycemic control or complication rates and may increase the risk of hypoglycemia.** If supplemental insulin is not necessary to correct mild-moderate hyperglycemia, inpatient management of hyperglycemia in patients with T2DM may be simplified, may reduce the risk of hypoglycemia and save costs.

Specific Aim: To test whether correction of mild-moderate hyperglycemia (BG > 140 mg/dL) with supplemental doses of rapid-acting insulin analogs improves glycemic control, complication rates, and rates of hypoglycemia in hospitalized patients with type 2 diabetes treated with basal bolus insulin regimen. Patients with T2DM admitted to the hospital receiving basal bolus therapy will be randomized to receive insulin correction before meals and at bedtime for BG >140 mg/dL, while others will be followed without insulin supplementation except for severe hyperglycemia (BG > 260 mg/dL).

Table 1: Total and Supplemental Insulin needs in Basal Bolus Arm of RCT

Trial	Number	Mean TDD Insulin	Mean daily SSI
RABBIT 2D (7)	65	42 units/day	5 units/day
RABBIT 2 Surgery (6)	104	33 units/day	9 units/day
POC Study	206	42 units/day	6 units/day
Basal-Plus (11)	144	32 units/day	7 units/day
DEAN Trial (12)	67	57 units/day	8 units/day

II. BACKGROUND AND CURRENT STATUS OF WORK IN THE FIELD.

Inpatient Glycemic Control in non-ICU setting. A large body of evidence suggests that in hospitalized patients with and without diabetes, the presence of hyperglycemia is associated with increased risk of complications and death (2-5; 15-20). Prospective RCTs in critical care patients have shown that aggressive glycemic control reduces short- and long-term mortality, multi-organ failure, systemic infections, and length of hospital and ICU stay [7, 9-11]. Similar complication reductions has been shown in patients admitted to general medicine and surgery services as well. In the non-ICU setting, practice guidelines for the management of hyperglycemia in patients with T2DM favor the use of physiologic (basal-nutritional-correction dose) insulin regimens over sliding scale regular insulin (SSRI) (4; 5). Several RCTs have shown that a basal bolus regimen improves glycemic control and reduces hospital complications in general medicine and surgery patients with T2DM (5-7; 21; 22).

Treatment with basal insulin glargine alone or in combination with rapid-acting insulin analogs before meals (basal bolus regimen) result in fairly constant BG values during the day (see preliminary data below). We have shown that with the exception of a small and non-significant rise in BG concentration before lunch (noontime), treatment with glargine insulin allows 24 hours of BG control with low rates of hypoglycemia, severe hyperglycemia and minimal requirement of insulin supplements (~5-9 U/day) (6; 7). In particular, our data indicate that BG concentration remains relatively constant during the evening with a low rate of severe hyperglycemia (0.1% of BG >400 mg/dl) despite minimal use of insulin supplements (see preliminary data). This small dose of supplemental insulin used in our previous studies raises the question of its necessity as part of a basal bolus regimen.

Several RCT have shown that hypoglycemia occurs in 12% and 33% of general medicine and surgery patients treated with basal bolus insulin regimens, respectively (6; 7; 11; 12). In the RABBIT-surgery trial (6), general surgery patients were treated with a total insulin dose of 0.5 unit/kg/day, given half as glargine once daily and half as glulisine before meals. A total of 17% of patients had a BG <70 mg/dL and 4% had a value <40 mg/dL. More recently, the Basal Plus trial (11) reported that 12% and 5% of patients treated with basal bolus with glargine and glulisine or with basal plus correction (supplements), respectively, had a BG <70 mg/dL and

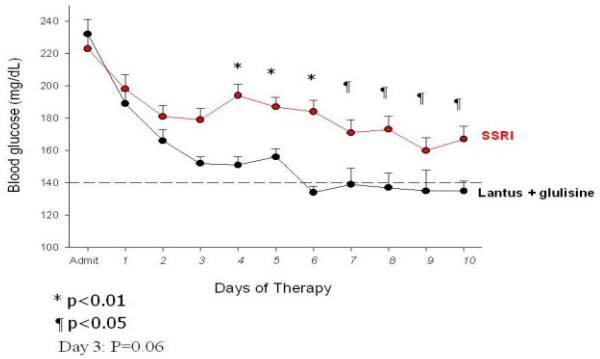
only 1% had a BG <40 mg/dL. In the DEAN trial (12), a basal-bolus regimen using detemir and aspart vs. NPH and regular insulin reported that ~one-third of patients had a BG < 60 mg/dl (12). Minimizing hypoglycemic events is of major importance in hospitalized patients because it has been shown to be an independent risk factor of poor outcome (23-25). It is not known, however, if the use of insulin supplements may have an impact on the overall rate of hypoglycemia in patients treated with basal bolus insulin regimen.

Significance and Innovation: Inpatient hyperglycemia is reported in up to 30% of general medicine and surgical patients. Our data indicate that in patients treated with basal (glargine or detemir) insulin, BG values remain relatively flat, without significant differences in use of insulin supplements or rate of hypoglycemia (6; 7). Moreover, in a recent study, we showed that there were no differences in glycemic control or hypoglycemic episodes with or without the correction of mild to moderate hyperglycemia with supplemental insulin at bedtime. All of our RCTs showed that supplemental insulin needs are small and are only between 6-9 units/day. However, no previous studies have determined if the use of supplemental insulin to correct hyperglycemia results in a change in glycemic control or hypoglycemia rates. It is possible that avoiding correction of mild to moderate hyperglycemia with supplemental insulin may result in lower rates of hypoglycemia and significant cost in hospitalized patients with T2DM treated with basal insulin analogs. *Accordingly, the proposed pilot study will provide novel and clinically useful information by determining if insulin supplementation will improve glycemic control and prevent hypoglycemia in insulin treated patients with T2DM. If insulin supplementation is not necessary for glycemic control, this may result in simplified insulin regimens, potentially reduce hypoglycemic episodes and save costs.*

Preliminary Data:

Our research team recently reported the results of four prospective, multi-center RCT comparing the efficacy and safety of different insulin regimens in T2DM patients admitted to general medicine and surgical services (6; 7; 11; 12). We have shown that a basal bolus regimen results in improved glycemic control compared to SSRI. In particular, these trials showed that the amount of supplemental insulin needed is very low.

Fig 1

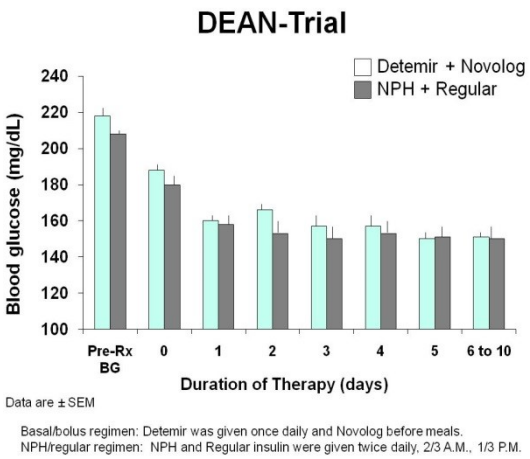


Umpierrez et al, Diabetes Care 30:2181–2186, 2007

In the Rabbit trial (Fig 1), 130 nonsurgical insulin naïve patients were randomized to receive glargine once daily and glulisine before meals (basal bolus) or SSRI before meals and at bedtime. Of these, 65 patients treated with glargine/glulisine (basal bolus) had greater improvement in BG control than SSRI with minimal risk of patients with

hypoglycemic events (3% of patients in each group had a BG < 60 mg/dL). A BG target of < 140 mg/dL was achieved in 66% of patients treated with glargine and glulisine whereas only 38% of those treated with SSRI achieved target glycemia. In this study, patients in the basal bolus arm required total insulin of 42 units/day. Of this, only 5 units/day were needed as supplemental insulin (Table 1).

Fig 2



In the DEAN trial (12), 130 patients with T2DM were treated with detemir once daily and aspart before meals (n=67) or with a split-mixed regimen of NPH and regular insulin twice daily (n=63) (Figure 2). Both regimens resulted in equivalent glycemic control and a similar rate of hypoglycemic events. A BG target <140 mg/dL before meals was achieved in 45% of patients in the detemir/aspart group and in 48% in the NPH/regular group. The TDD of insulin in the detemir arm was 57 units/day and of that the supplemental dose was only 8 units/day.

In the Rabbit-Surgery trial (Figure 3), 211 general non-cardiac surgery patients with T2DM were randomized to a basal bolus regimen with glargine once daily and glulisine before meals (n=104) or to SSRI before meals (n=107). Study outcomes included differences in daily BG levels and a composite of hospital complications including postoperative wound infection, pneumonia, respiratory failure, acute renal failure, and bacteremia. The mean daily glucose after the 1st day of BB and SSRI was 145±32 mg/dl and 172±47 mg/dl, respectively, p<0.01. BG readings <140 mg/dl were recorded in 55% of patients in basal bolus and 31% in the SSRI group, p<0.001. There were reductions with basal bolus as compared with SSRI in the composite outcome (24.3% and 8.6%, OR: 3.39 (95% CI: 1.50-7.65); p=0.003). We concluded that treatment with basal improved glycemic control and reduced hospital complications compared to SSRI in surgery patients with T2DM. The TDD of insulin in the basal bolus group was 33 units daily with 9 units/day of supplemental insulin. The basal bolus group in this study received more supplemental insulin than patients in the basal bolus arms of our other RCTs. This is likely because ~ 30% of patients in the Rabbit-Surgery trial underwent abdominal surgery and were likely

Figure 3. Postoperative Complications

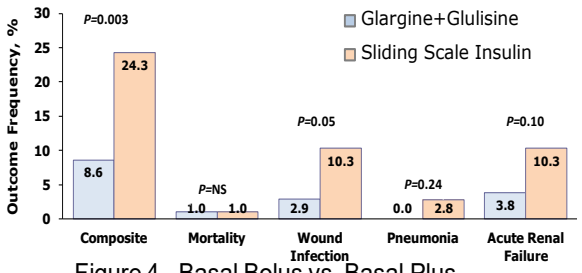


Figure 4. Basal Bolus vs. Basal Plus

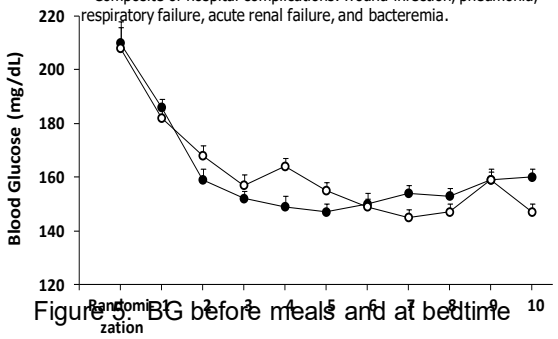
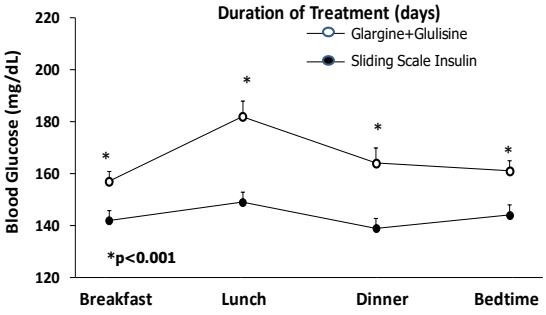


Figure 5. BG before meals and at bedtime



NPO. These patients did not receive prandial insulin and therefore the supplemental dose may have been higher.

In the Basal Plus trial (11), we compared the effect of a daily dose of glargine with correction doses of glulisine to a standard basal bolus regimen in 300 medical and surgical patients with T2DM. We observed similar mean daily BG (Figure 4), pre-meal glucoses (Figure 5) and hypoglycemic events. There were no differences in length of hospital stay or hospital complications between patients treated with basal plus and basal bolus insulin regimen. These results indicate that a simple regimen of a daily basal dose of glargine plus correction doses with glulisine before meals (as needed) is an alternative to basal bolus insulin and results in similar glycemic control and hypoglycemia in general medicine and surgery patients with T2DM. In the basal bolus arm of the study, TDD of insulin was 32 units/day and of this only 7 units/day was given as supplemental dose.

Figure 6: Mean Daily Fasting Glucose

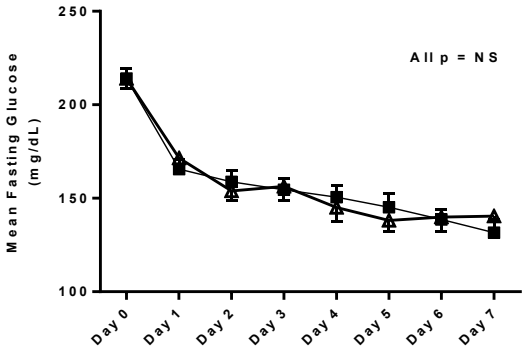
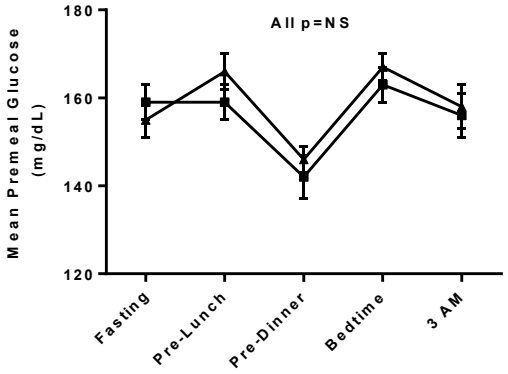


Figure 7: Premeal Glucose Levels



In a recently completed study (POC) (13), we found that not correcting mild to moderate hyperglycemia at bedtime did not change fasting daily glucose levels (Figure 6). Further, there were no changes in mean daily glucose, pre-meal glucose or hypoglycemic events (Figure 7). In this study, TDD of insulin was 42 units/day. Of this, only 6 units/day was required as a supplemental dose.

Frequency of hypoglycemia and hyperglycemia during basal insulin treatment. The frequency of mild hypoglycemia (BG<70 mg/dl) and severe hypoglycemia (BG<40 mg/dl) at bedtime among 2,377 patients recruited in different randomized control trials conducted by our research team is less than 1.5% and 0.5%, respectively. The frequency of hypoglycemia is low in comparison to patients treated with sulfonylureas (26). Similarly, the frequency of severe hyperglycemia (BG>400 mg/dl) is remarkably low (0.08%) among insulin treated patients with T2DM (6; 7).

In summary, during the past decade our research group has provided novel and important information to guide health care providers in inpatient management of patients with hyperglycemia and diabetes. Our preliminary data indicate that the use of basal insulin alone or in combination with rapid-acting insulin analogs (basal bolus regimen) in non-ICU patients with T2DM improves glycemic control and reduces the rate of hypoglycemia. In addition, our studies

have shown that BG values remain relatively constant during the day and that the need for supplemental insulin is low in comparison to the TDD of insulin required.

IV. Experimental Plan:

Specific Aim: To test whether correction of mild-moderate hyperglycemia (140-260 mg/dL) with supplemental doses of rapid-acting insulin analogs improves glycemic control, complication rates, and rates of hypoglycemia in patient with type 2 diabetes treated with basal bolus insulin regimen**.**

IV.a. **Study Design and Methods:**

A total of 250 general medicine and surgery patients with T2DM treated with basal bolus insulin regimen will be included in this pilot RCT. Half of the patients will be randomized to receive insulin supplements before meals and at bedtime for BG >140 mg/dL, while the other half will be followed without insulin supplementation except for severe hyperglycemia (BG > 260 mg/dL).

IV.b. Primary and Secondary Outcomes:

The primary outcome of the study is to compare differences in mean daily BG levels between patients receiving insulin supplementation for correction of hyperglycemia (BG > 140 mg/dL) compared to those without insulin supplementation except for correction of severe hyperglycemia (BG > 260 mg/dL).

Secondary outcomes include differences between treatment groups in any of the following measures: 1) mean BG before meals, bedtime and 3 AM; 2) number of BG within target; 3) number of hypoglycemia (BG < 70 mg/dl); hyperglycemia (BG > 260 mg/dL during the day or BG>350 mg/dl at bedtime); 4) daily dose of insulin; 5) length of hospital stay and mortality; 6) hospital complications (nosocomial infections, pneumonia, bacteremia, respiratory failure, and acute kidney injury [rise of serum creatinine >0.5 mg/dL (or 50%) of baseline value]), 7) hypoglycemia symptom assessment in both groups.

IV.c. Research Plan.

Patients with T2DM admitted with acute or chronic medical illnesses or for elective and emergency surgical illness or trauma would be considered candidates in this study. The goal of insulin therapy is to maintain a fasting and pre-meal BG<140 mg/dL while avoiding hypoglycemia. Diabetic patients admitted to general medical or surgery areas with a BG > 140 mg/dL and < 400 mg/dL will be randomized (using a randomization table) to:

Group 1. Basal bolus insulin regimen *with* corrective doses of aspart/lispro insulin for BG > 140 mg/dL (n = 125).

Group 2. Basal bolus insulin regimen *without* corrective doses of aspart/lispro insulin except for BG > 260 mg/dL (n = 125).

The primary medical team (PMT) will decide on the treatment for the surgical and other medical problem(s) for which patients are admitted. The study team will provide recommendations for discharge as outlined below but will leave it up to the discretion of the PMT. The PMT can also decide the medical treatment at discharge including the use of insulin or oral antidiabetic agent(s), patient's discharge orders and referral to the diabetes clinic at discharge.

IV.d. Basal Bolus Insulin Protocol.

Patients will be started on basal bolus insulin therapy as previously reported (6; 7; 11; 13). In brief, subjects treated with insulin prior to admission will receive 80% of the outpatient insulin dose. Insulin-naïve patients will discontinue oral agents and will receive a starting total daily dose (TDD) of insulin of 0.4 U/kg/day for BG between 140-200 mg/dL and 0.5 U/kg/day for BG between 201-400 mg/dL. The starting TDD will be 0.3 U/kg/day in patients ≥70 yrs or with an eGFR < 60 ml/min. Half of TDD will be given as glargine or detemir once daily and half as meal time insulin (aspart or lispro) divided in three equal doses before meals. Insulin dose will be adjusted daily to maintain a fasting and pre-dinner BG between 100-140 mg/dL (6; 7).

Supplement insulin given as aspart or lispro will be given following a "supplemental insulin scale" protocol (6; 7; 27). Patients randomized to Group 1 will receive supplements to correct BG > 140 mg/dL, and those in Group 2 will not receive supplements except for correction of hyperglycemia (BG>260 mg/dL). Corrective doses for bedtime in group 1 will be given for BG > 220 mg/dL.

Group 1. Basal bolus regimen with corrective doses of rapid-acting insulin prior to meals.

Patients Treated with Insulin Prior to Admission

- Subjects receiving insulin therapy will receive 80% of the total daily outpatient insulin dose. For subjects receiving glargine, detemir, regular, lispro, glulisine or aspart, the total daily insulin dose prior to admission will be switched to basal insulin (glargine or detemir)/ meal time insulin (aspart/lispro) combination on a unit-for-unit basis.
- Half of total daily dose will be given as basal insulin (glargine or detemir) insulin and half as meal time insulin (aspart/lispro) insulin.
- Basal insulin (glargine or detemir) insulin will be given once daily, at the same time of the day.
- Patients will receive the full-dose of basal insulin (glargine or detemir) (even if NPO) the day of surgery or diagnostic procedure(s).
- Meal time insulin (aspart/ lispro) insulin will be given in three equally divided doses before each meal. To prevent hypoglycemia, if a subject is not able to eat, the dose of meal time insulin (aspart/lispro) will be held.

Patients Treated with Oral Agents Prior to Admission

- Oral antidiabetic drugs (sulfonylureas, repaglinide, nateglinide, metformin, pioglitazone, DPP4 inhibitors) and non-insulin injected antidiabetic drugs (pramlinitide, exenatide, liraglutide) will be discontinued on admission.

- **Starting total daily insulin dose:**
  - 0.4 units per kilogram of body weight per day when the blood glucose concentration at randomization is between 140-200 mg/dL.
  - 0.5 units per kilogram of body weight per day blood glucose concentration at randomization is between 201-400 mg/dL
  - The starting insulin TDD will be reduced to 0.3 units per kg in patients ≥ 70 years of age and/or with an eGFR < 60 ml/min.
- Half of total daily dose will be given as basal insulin (glargine or detemir) and half as meal time insulin (aspart/lispro).
- Basal insulin (glargine or detemir) will be given once daily, at the same time of the day.
- Patients will receive the full-dose of basal insulin (glargine or detemir) insulin (even if NPO) the day of surgery or diagnostic procedure(s).
- Meal time insulin (aspart/lispro) will be given in three equally divided doses before each meal. To prevent hypoglycemia, if a subject is not able to eat, the dose of aspart/lispro will be held.

Supplemental insulin. Aspart/lispro insulin will be administered following the "supplemental insulin scale" protocol.

- If a patient is able and expected to eat all or most of his/her meals, supplemental aspart or lispro insulin will be administered before each meal and at bedtime following the "usual" dose of the supplemental insulin scale protocol.
- If a patient is not able to eat, supplemental aspart or lispro insulin will be administered every 6 hours following the "sensitive" dose of the supplemental insulin scale protocol.

Insulin adjustment.

- Daily insulin dose will be adjusted as follow:
  - If the fasting and/or pre-dinner BG is between 100 - 140 mg/dL in the absence of hypoglycemia the previous day: no change
  - If the fasting and/or pre-dinner BG is between 140 - 180 mg/dL in the absence of hypoglycemia: increase basal insulin by 10% every day
  - If the fasting and/or pre-dinner BG is >180 mg/dL in the absence of hypoglycemia the previous day: increase basal insulin dose by 20% every day
  - If the fasting and/or pre-dinner BG is between 70 - 99 mg/dL in the absence of hypoglycemia: decrease TDD (basal and prandial) insulin dose by 10% every day
  - If a patient develops unexplained hypoglycemia (BG <70 mg/dL), the insulin TDD (basal and prandial) should be decreased by 20%.

Supplemental Insulin (aspart/lispro) prior to meals:

<u>BEFORE MEAL,</u> Supplemental Sliding Scale Insulin (number of units) - Add to scheduled insulin dose.

Blood Glucose (mg/dL)	Sensitive	Usual	Resistant
≤ 140	0	0	0
>141-180	2	3	4
181-220	3	4	6
221-260	4	5	8
261-300	5	6	10
301-350	6	8	12
351-400	7	10	14
> 400	8	12	16

<u>BEDTIME.</u> Give half of Supplemental Sliding Scale Insulin.

Blood Glucose (mg/dL)	Sensitive	Usual	Resistant
<221	0	0	0
221-260	1	2	4
261-300	2	3	5
301-350	3	4	6
351-400	4	5	7
> 400	5	6	8

The patient's inpatient primary medical or surgical team may change insulin dose at their discretion in the presence of hypoglycemia (BG <70 mg/dL) or severe hyperglycemia (BG >350 mg/dL). In addition, the attending and/or study physician may consider using the total supplemental insulin dose, patient's nutritional intake, and results of BG testing to adjust insulin regimen.

Blood glucose monitoring. BG will be measured before each meal, at bedtime and/or 3 AM (or every 6 hours if a patient is not eating) using a glucose meter. In addition, blood glucose will be measured at any time if a patient experiences symptoms of hypoglycemia or if requested by the treating physician. The nursing staff or a research team staff will record all glucose readings in the hospital's blood glucose flow-sheet (electronic chart).

Group 2. Basal Bolus insulin regimen without corrective doses of rapid-acting insulin prior to meals

Patients Treated with Insulin Prior to Admission

- Subjects receiving insulin therapy will receive 80% of the total outpatient insulin dose. For subjects receiving glargine, detemir, regular, lispro, glulisine or aspart, the total daily insulin dose prior to admission will be switched to basal insulin (glargine or detemir) and meal time insulin (aspart/lispro) combination on a unit-for-unit basis.
- Basal insulin (glargine or detemir) will be given once daily, at the same time of the day.
- Patients will receive the full-dose of basal insulin (glargine or detemir) (even if NPO) the day of surgery or diagnostic procedure(s).
- Meal time insulin (aspart/lispro) will be given in three equally divided doses before each meal. To prevent hypoglycemia, if a subject is not able to eat, the dose of aspart/lispro will be held.

Patients Treated with Oral Agents Prior to Admission

- Oral antidiabetic drugs (sulfonylureas, repaglinide, nateglinide, metformin, Actos, DPP4 inhibitors) and non-insulin injected antidiabetic drugs (pramlinitide, exenatide) will be discontinued on admission.
- **Starting total daily insulin dose:**
  - 0.4 units per kilogram of body weight per day when the admission and/or blood glucose concentration at randomization is between 140-200 mg/dL
  - 0.5 units per kilogram of body weight per day when the admission and/or mean blood glucose concentration is between 201-400 mg/dL
  - The starting insulin TDD will be reduced to 0.3 units per kg in patients ≥ 70 years of age and/or with an eGFR < 60 ml/min.
- Half of total daily dose will be given as basal insulin (glargine or detemir) and half as meal time insulin (aspart or lispro).
- Basal insulin (glargine or detemir) will be given once daily, at the same time of the day.
- Patients will receive the full-dose of basal insulin (glargine or detemir) (even if NPO) the day of surgery or diagnostic procedure(s).
- Meal time insulin (aspart/lispro) will be given in three equally divided doses before each meal. To prevent hypoglycemia, if a subject is not able to eat, the dose of aspart/lispro will be held.

Supplemental insulin. Aspart or lispro insulin will be administered following the "supplemental insulin scale" protocol before meals.

- If a patient is able and expected to eat all or most of his/her meals, supplemental (aspart or lispro) insulin will be administered before each meal following the "usual" dose of the supplemental insulin scale.
- If a patient is not able to eat, supplemental (aspart/lispro) insulin will be administered every 6 hours following the "sensitive" dose of the supplemental insulin scale protocol.

Insulin adjustment. Daily insulin dose will be adjusted as follow:

- If the fasting and/or pre-dinner BG is between 100 - 140 mg/dL in the absence of hypoglycemia the previous day: no change
- If the fasting and/or pre-dinner BG is between 140 - 180 mg/dL in the absence of hypoglycemia: increase basal insulin by 10% every day
- If the fasting and/or pre-dinner BG is >180 mg/dL in the absence of hypoglycemia the previous day: increase basal insulin dose by 20% every day
- If the fasting and/or pre-dinner BG is between 70 - 99 mg/dL in the absence of hypoglycemia: decrease basal and prandial insulin TDD by 10% every day
- If a patient develops unexplained hypoglycemia (BG <70 mg/dL), the basal and prandial TDD insulin should be decreased by 20%.

Insulin supplementation (aspart or lispro) prior to meals:

BEFORE MEAL, Supplemental Sliding Scale (number of units) - Add to scheduled insulin dose.

Blood Glucose (mg/dL)	Sensitive	Usual	Resistant
< 260	0	0	0
261-300	5	6	10
301-350	6	8	12
351-400	7	10	14
> 400	8	12	16

BEDTIME. Give half of Supplemental Sliding Scale Insulin

Blood Glucose (mg/dL)	Sensitive	Usual	Resistant
< 260	0	0	0
261-300	2	3	5
301-350	3	4	6
351-400	4	5	7
> 400	5	6	8

The attending physician may change insulin dose as his/her discretion in the presence of hypoglycemia (BG <70 mg/dL) or severe hyperglycemia (BG >350 mg/dL). In addition, the attending and/or study physician may consider using the total supplemental insulin dose, patient's nutritional intake, and results of BG testing to adjust insulin regimen.

Blood glucose monitoring. BG will be measured before each meal, at bedtime and 3 AM (or every 6 hours if a patient is not eating) using a glucose meter. In addition, blood glucose will be measured at any time if a patient experiences symptoms of hypoglycemia or if requested by the treating physician. The nursing staff or a research team staff will record all glucose readings in the hospital's blood glucose flow-sheet (chart).

IV.f. Inpatient Hypoglycemia Management:

For blood glucose < 70 mg/dL, follow hypoglycemia orders below:

- If patient is alert and can tolerate oral intake, give 20 grams of fast-acting carbohydrate (6 oz. fruit juice or regular soda, crackers).
- If patient not alert and CANNOT tolerate oral intake, give1ampule (50 mL) of D_{50}.
- Check finger-stick BG q 15 minutes and repeat above treatment until BG > 100 mg/dL.
- Once BG > 100 mg/dL, repeat finger-stick BG 1 hour later and treat as follows:
  - If BG < 70 mg/dL, call MD and follow Hypoglycemia Orders (above)
  - If BG 70 – 100 mg/dL, give snack/scheduled meal and recheck BG q 1 hr until BG > 100 mg/dL.
  - If BG > 100, no further treatment needed.

IV.g. Treatment recommendations at discharge. Treatment of diabetes at discharge will not be part of the current research proposal; however, the following guide based on admission HbA1c will be shared with primary team to help guiding outpatient insulin therapy:

- **Admission A1C < 7% prior to admission:**
  - Discharge on same pharmacologic regimen (oral agents, insulin therapy).
  - Assure there are no contraindications to oral agents (i.e., TZDs and heart failure; metformin and renal failure).
- **Admission A1C between 7% and 10% prior to admission:**
  - Discharge on once daily basal insulin (glargine or detemir) insulin.
  - If no contraindications to oral agents restart oral agents in addition to basal insulin (glargine or detemir) at 50% to 80% of total daily hospital dose.
  - Patients not to be treated with oral agents should be instructed to continue taking 100% of inpatient daily dose of glargine (as monotherapy).
- **Admission A1C ≥ 10% prior to admission:**
  - Discharge on basal bolus regimen at same inpatient total daily insulin dose.
    - Basal insulin (glargine or detemir) once daily, at the same time of the day.
    - Rapid-acting insulin (aspart/lispro) before meals.
  - Alternative: If no contraindications to oral agents (i.e., TZDs and heart failure; metformin and renal failure) restart oral agents in addition to glargine or detemir once daily at 80% of total daily hospital dose.

V. METHODS and PROCEDURES APPLIED to HUMAN SUBJECTS:

V.a. Subject Population/Inclusion Criteria. We plan to study a total of 250 male and female patients with a known history of T2DM for >3 months, age 18-80 yr, treated with either diet alone, any combination of oral antidiabetic agents, non-insulin injectables or insulin therapy. Subjects must have a BG >140 mg and <400 mg/dL without laboratory evidence of diabetic ketoacidosis (28).

Exclusion Criteria. Subjects with hyperglycemia without a history of diabetes, acute critical illness admitted to the ICU or expected to require ICU admission; receiving continuous insulin infusion, clinically relevant hepatic disease, corticosteroid therapy, creatinine ≥ 3.5 mg/dL and/or GFR <30, subjects unable to sign consent, and pregnancy which will be excluded by a urine pregnancy test.

V.b. Study Sites: The study will be conducted at Grady Memorial Hospital and Emory University Hospitals (EUH and EUHM).

VI. CLINICAL MANAGEMENT GUIDELINES

V.I.a. Treatment of Hypoglycemia. Hypoglycemia, defined as a BG level < 70 mg/dL will be treated following standard hypoglycemia protocols available at our institutions (6; 7; 29).

V.I.b. Assessment and Monitoring of Hospital Complications and Mortality. The research team will follow patients daily in order to determine presence of infectious and non-infectious complications. Nosocomial infections will be diagnosed based on standardized CDC criteria (30).

VII. Data Analysis. The primary endpoint of this study is mean fasting BG concentration between treatment groups. We set the equivalence margin in our non-inferiority hypothesis for comparing treatment effect as 18 mg/dL (1 mmol/l). Based on previous studies (6; 7), we anticipate a standard deviation of mean fasting BG~50 mg/dL. With a one-sided, two-sample t-test, 123 subjects would be required for each group to achieve 80% power to detect non-inferiority. Here we conservatively set the significance level as 0.025 to ensure sufficient power when a two-sided test is used for the primary outcome, we will perform cross-sectional analyses using one-way ANOVA or linear models, followed by repeated measures ANOVA or linear models to estimate difference between treatment groups while simultaneously examining mean fasting BG across multiple days during treatment. Similar analyses will be conducted for continuous secondary outcomes. Chi-square tests (or Fisher's Exact test), Logistic regression, and Poisson regression will be conducted to analyzed discrete secondary outcomes. A p-value of <0.05 is considered significant. We expect a very low attrition rate in the proposed study. Therefore, a total of 250

patients (125 patients per group) will be recruited in this pilot study. The proposed methods will be implemented by SAS (v9.2).

VIII. Protection against risks.

VIII.a. Hypoglycemia. We expect that <10% of subjects will experience episodes of hypoglycemia. To minimize the risk, outpatient dose of insulin will be reduced by 20% on admission; and insulin naïve patients ≥ 70 years of age and/or with an eGFR < 60 will be started at a TDD of 0.3 U/kg/day.

VIII.b. Severe hyperglycemia. Patients with persistent hyperglycemia (≥3 consecutive BG readings > 260 mg/dL or a mean daily BG ≥ 260 mg/dL) after the 1st day of treatment will be considered as treatment failure and will be switched to continuous insulin infusion if needed. Patients randomized to group 1 will receive insulin supplements for BG>140 mg/dL. Those randomized to group 2 will receive insulin supplements only when BG > 260 mg/dL. We anticipate that less than 1% of patients will experience severe hyperglycemic episodes (BG > 350 mg/dL).

VIII.c. Data and Safety Monitoring Plan (DSMP).
The DSM committee will review unblended data on safety, treatment compliance, and evaluate the efficacy of the intervention being studied in this clinical trial. The DSMC will meet at 6-month intervals and report on study progress to the IRB.

VIII.d. Interim Analysis and Stopping Rules. An independent data safety and monitoring board will assess hospital complications and severe hypoglycemic events. The trial will be stopped if there is evidence beyond a reasonable doubt of a difference between groups on hospital complications (two-sided alpha level, <0.01) or if severe hypoglycemic events (<40 mg/dL) are >20%.

IX. Timetable. Our research team has extensive experience in conducting prospective RCTs comparing different insulin regimens in T2DM. We have postdoctoral fellows and research coordinators in the 2 hospitals affiliated with Emory University. Based on our experience, we can recruit 4 to 8 medical/surgical patients with T2DM per week, thus we anticipate completing recruitment in 12 to 18 months.

X. Potential Benefits to the Subject. We believe that all subjects will benefit greatly from this study. Intensified BG monitoring and glycemic control may significantly reduce hospital complications associated with hyperglycemia and hypoglycemia.

XI. Potential Benefits to Society. This study will provide clinically useful information by determining benefits of insulin supplementation prior to meals in improving glycemic control and in reducing hypoglycemia in insulin treated patients with T2DM.

XII. Risk/Benefit Assessment. Insulin therapy is the mainstay of diabetes management in medical and surgical patients with diabetes. There are no prospective, randomized studies to assess the benefits of insulin supplementation in non-ICU patients with T2DM treated with a basal bolus regimen. Basal bolus regimen has been shown to be effective in general medicine and surgery patients; however, some patients may experience mild and moderate hypoglycemia.

XIII. Therapeutic Alternatives. Patients can be treated with oral pharmacological agents and several different types of insulin are currently available at Grady Hospital and Emory University Hospital and other institutions for the treatment of T2DM.

XIV. Inclusion of women. We anticipate that ~50% of the study subjects will be female. No patients under the age of 18 and no pregnant women will be included in the study. Absence of pregnancy must be demonstrated by blood or urine testing if clinically indicated (i.e., female subjects of child bearing potential).

XV. Inclusion of minorities. Patients will not be excluded based on race or ethnic origin. We anticipate that approximately one-third of patients will be African Americans, Hispanics, and Caucasians.

XVI. Inclusion of children. No patients under the age of 18 will be recruited in this study.

XVII. Confidentiality. Informed consent will follow the procedure of Emory University Institutional Review Board. Every potential participant will be informed in writing and verbally with the important key points of the study. One of the investigators or research coordinators will obtain a witnessed informed consent prior to inclusion of a patient into the study. Data collection records with personal identifiers will be stored in locked file cabinets. Presentation of the study results at regional or scientific meetings or in publications will not identify subjects. Access to research and confidential records will be limited to clinical investigators, coordinators, and the IRB at Emory University.

XVIII. Payment for Participation. Participation in this study is voluntary. Patients will receive twenty dollars ($20.00) prior to discharge. If a participant should stop participation before completion, the payment will be prorated at $10.00 per day to a maximum of twenty dollars ($20.00).

XIX. Financial Obligation. No additional cost to patients or to the institution will be incurred for research purposes. Glargine, detemir, aspart and lispro are formulary drugs and represent the standard of care in our institutions. Glargine detemir, aspart and lispro, syringes, glucose meter and strips, and oral antidiabetic drugs will not be provided as part of the study.

XX. Research Injuries. If a patient is injured because of taking part in this study, Dr. Vellanki along with the Emory Co-Investigators with the medical facility will make medical care available to the patient at patient's own cost. Financial compensation for such things as lost wages, disability or discomfort due to an injury related to the study is not available.

XXI. Financial Conflict of Interests. None of the investigators in this study have any outside activities that may represent a conflict of interest. None of the investigators have an economic interest in an outside entity, or act as officers, directors, employees or consultants with such an entity, whose financial interest may be affected by this research study.

XXII. Informed Consent. After identification of eligible patients these individuals will be provided basic information regarding the study and, if interested, they will then be screened by research staff using the inclusion/exclusion criteria delineated elsewhere in this protocol. The consent form, potential risks and benefits, and the rights of research participants will be explained to the participant by the investigators or research coordinator. Individuals will be asked if they have any questions, and if present, questions will be answered by research staff. The principal investigator will also be available at all times to answer questions that participants may have during the consent procedure or during the time a participant is enrolled in the study. The consent form will be completed in accordance with the IRB guidelines of Emory University. A signed copy of the consent form will be provided to the participant and a copy will be placed in the file that is maintained for each participant in the study office.

XXIII. Medical Device Research. Not applicable.

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