Sitagliptin for the prevention of stress hyperglycemia in patients without diabetes undergoing coronary artery bypass graft (CABG) surgery

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ABSTRACT

Aims To determine if treatment with sitagliptin, a dipeptidyl peptidase-4 inhibitor, can prevent stress hyperglycemia in patients without diabetes undergoing coronary artery bypass graft (CABG) surgery.

Methods We conducted a pilot, double-blinded, placebo-controlled randomized trial in adults (18–80 years) without history of diabetes. Participants received sitagliptin or placebo once daily, starting the day prior to surgery and continued for up to 10 days. Primary outcome was differences in the frequency of stress hyperglycemia (blood glucose (BG) >180 mg/dL) after surgery among groups.

Results We randomized 32 participants to receive sitagliptin and 28 to placebo (mean age 64±10 years and HbA1c: 5.6%±0.5%). Treatment with sitagliptin resulted in lower BG levels prior to surgery (101±mg/dL vs 107±13 mg/dL, p=0.01); however, there were no differences in the mean BG concentration, proportion of patients who developed stress hyperglycemia (21% vs 22%, p>0.99), length of hospital stay, rate of perioperative complications and need for insulin therapy in the intensive care unit or during the hospital stay.

Conclusion The use of sitagliptin during the perioperative period did not prevent the development of stress hyperglycemia or need for insulin therapy in patients without diabetes undergoing CABG surgery.

Significance of this study

What is already known about this subject?

► Stress hyperglycemia is very frequent in patients without diabetes undergoing coronary artery bypass graft (CABG).

What are the new findings?

► The use of sitagliptin in patients without diabetes undergoing CABG did not reduce the frequency of stress hyperglycemia in the intensive care unit (ICU), but was associated with lower insulin requirements during continuous insulin infusion in the ICU, and was safe and well tolerated in participants undergoing CABG surgery.

How might these results change the focus of research or clinical practice?

► We found minor differences in glucose levels before surgery and total insulin dose in the ICU among patients without diabetes exposed to sitagliptin. These differences, however, are unlikely to be clinically significant.

► Our preliminary results do not justify the conduction of a larger clinical trial in patients without diabetes.

INTRODUCTION

Stress hyperglycemia (blood glucose (BG) >140 mg/dL) is a common finding in patients with and without a history of diabetes (diabetes mellitus, DM) after cardiac surgery[1] reported in 80% of patients with diabetes and in more than 50% of patients without history of diabetes after cardiac surgery.[2 3] Perioperative hyperglycemia in patients with and without DM is associated with higher perioperative mortality,[4–6] deep sternal wound infections,[7 8] acute renal failure,[1] postoperative strokes,[9 10] longer hospital stays,[4 10] and higher healthcare resource utilization.[11–13]

In surgical patients, stress hyperglycemia has been arbitrarily defined as an increase in BG above 180 mg/dL in patients without previously diagnosed diabetes.[14–16] Stress hyperglycemia results from the acute metabolic and hormonal changes associated with the response to injury, anesthesia, and stress.[17] Although it has long been considered an adaptive stress response which is beneficial for survival, stress hyperglycemia is associated with a fourfold increased risk of complications compared with patients with normoglycemia and with a twofold higher complications compared with patients with a known history of diabetes.[16 18–22]

Clinical guidelines recommend the use of continuous intravenous insulin infusion (CII) for treatment of stress hyperglycemia

in cardiac surgery patients.[23–26] Although effective and widely utilized,[27–29] the use of CII is labor intensive, requiring hourly BG testing and insulin drip adjustment, and is associated with a significant risk of hypoglycemia, reported in 5%–32% of patients in the intensive care unit (ICU).[30–33] Recently, we and others have reported that therapy with dipeptidyl peptidase-4 (DPP-4) inhibitors is an effective strategy to improve glycemic control in general medicine and surgical patients with type 2 diabetes with mild to moderate hyperglycemia (180–200 mg/dL).[34] Therefore, we explored if the DPP-4 inhibitor sitagliptin, by stimulating insulin secretion in a glucose-dependent fashion and by reducing glucagon-mediated hepatic glucose production, could prevent the development of stress hyperglycemia during the perioperative period in cardiac surgery patients without a history of diabetes.

SUBJECTS, MATERIALS, AND METHODS

We performed a single-center, pilot, prospective, double-blinded, randomized placebo-controlled study at four academic hospitals including Emory University Hospital, Emory Midtown Hospital, Emory Saint Joseph's, and Grady Memorial Hospital in Atlanta, Georgia, between January 2016 and October 2016.

Patient and public involvement

Patients were not invited to comment on the study design and were not consulted to develop patient-relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

We enrolled adult participants aged 18–80 years, without a history of diabetes, confirmed by HbA1c <6.5% (normal HbA1c <5.7%, pre-diabetes: HbA1c 5.7%–6.4%; diabetes: HbA1c ≥6.5%)[35] and fasting BG <126 mg/dL obtained prior to hospital admission and/or surgery. We excluded patients with a history of diabetes or previous treatment with antidiabetic therapy, patients with decreased renal function (estimated glomerular filtration rate (eGFR) <30 mL/min per 1.73 m²) or with clinically significant liver disease, gastrointestinal (GI) obstruction or adynamic ileus, clinically relevant pancreatic or gall bladder disease or patients treated with oral or injectable corticosteroids.

Participants were randomly assigned to sitagliptin or matched placebo once daily. Research pharmacists at each institution received a computer-generated randomization table to assign participants (1:1) from a statistician. All medical and/or surgical management decisions were under the responsibility of the primacy care team.

The study drug, sitagliptin or placebo, was given once daily, starting the day prior to surgery and continued until hospital discharge, or up to 10 days. Sitagliptin dose was adjusted according to eGFR, per manufacturer instructions: 100 mg/day if eGFR was ≥50 mL/min per 1.73 m², 50 mg/day if eGFR was <50 mL/min per 1.73 m²,

and 25 mg daily if the calculated GFR was <30 mL/min/1.73 m² during the study period. BG was measured every 30 min intraoperatively, and every 1–2 hours after arrival to ICU, until the patient was hemodynamically stable and could tolerate oral intake; at this point and after transition to regular floor, BG measurements were performed before each meal and at bedtime.

The primary outcome of the study was the difference in the frequency of stress hyperglycemia, defined as participants who had one or more episodes of BG >180 mg/dL, between participants treated with sitagliptin or placebo, after arrival to ICU. Secondary outcomes included differences in mean BG during the ICU stay, number of participants with persistent stress hyperglycemia after arrival to ICU, defined as two consecutive BG >180 mg/dL or with average daily BG >180 mg/dL, need for CII in the ICU, mean insulin dose of CII and duration during ICU stay (unit/hour/day and units/day).

We also compared the frequency of stress hyperglycemia including BG >140 mg/dL and BG >180 mg/dL, mean daily BG, and number of participants requiring subcutaneous insulin after transition from intravenous insulin, and number of participants with severe hyperglycemic events (BG >200 mg/dL) or with hypoglycemia (BG ≤70 mg/dL and <40 mg/dL). In addition, we explored differences in a composite of perioperative complications including sternal wound infection (deep and superficial), bacteremia, pneumonia (infection was confirmed by positive culture of blood, sputum, urine, pleural or mediastinal fluid, and/or incisional discharge), respiratory failure, acute kidney injury (serum creatinine increment level by >50% from baseline), major adverse cardiovascular events including acute myocardial infarction, stroke, heart failure and cardiac arrhythmias (significant arrhythmias were those that caused hemodynamic instability and required treatment). Stroke was described as a neurological abnormality that was confirmed by a CT scan and/or neurologist. Additionally, we compared differences between groups in hospital-related outcomes, including: length of stay (LOS) in the ICU and the hospital, in-hospital mortality, hospital readmissions and emergency room visits within 30 days after hospital discharge.

Participants on arrival to ICU had point-of-care testing (POCT) BG checks every 1–2 hours according to institutional protocol, those who developed stress hyperglycemia continued to receive the study drug (sitagliptin or placebo) and were started on insulin regimen, adjusted to achieve and maintain a BG target between 110 and 180 mg/dL following our standard hospital protocol (see online supplementary appendix 1).[36] Intravenous insulin was started with two values >180 mg/dL in the ICU and continued until the patient was able to eat and/or transferred to non-ICU settings. Once patients tolerate oral intake, it is recommended that patients have POCT BG before each meal and at bedtime. After transition, participants with two consecutive BG >180 mg/dL, or with average daily BG >180 mg/dL received rescue therapy

with subcutaneous basal (levemir or glargine) insulin once daily plus correction doses by sliding scale (see online supplementary appendix 2).[37]

Statistical analysis

This proof-of-concept proposal was a two-arm, randomized, placebo-controlled pilot clinical trial. In this pilot and proof-of-concept trial, we aimed to randomize a total of 60 patients scheduled to undergo cardiac surgery. Based on our recent GLUCO-CABG[38] trial, 81% of participants without a history of diabetes had stress hyperglycemia (BG >140 mg/dL) and 69% had at least one BG >180 mg/dL. In the power calculation, we assumed the same rate of stress hyperglycemia in the control (placebo) group, and anticipated that sitagliptin would reduce the rate of hyperglycemia by 25%–50% (corresponding to OR in the range of 0.36–0.16). Under these assumptions, with the sample size of 60 (ie, 30 per group), we would have 92%, 80%, and 41% power to detect effect sizes corresponding to OR=0.16, 0.21, and 0.36, respectively. The preliminary effect estimates obtained in this pilot study would provide the data to consider the design of larger trials with realistic event rates and effect sizes.

The primary endpoint was the frequency of stress hyperglycemia (>180 mg/dL) after surgery. We first used two-sided χ^2 test or Fisher's exact test to compare the rate of stress hyperglycemia and other categorical variables between the treatment group and the control group. We used non-parametric Kruskal-Wallis tests to compare continuous variables such as LOS or BG values. P values <0.05 are considered statistically significant. The data analyses were performed with SAS V.9.4.

RESULTS

Between January 2016 and October 2016, a total of 68 participants without history of diabetes signed the consent to participate in the study. Two participants were excluded because surgery was cancelled after percutaneous coronary intervention, four withdrew consent, one participant had the procedure rescheduled and did not receive study medication, and one participant was found to have a high HbA1c (see online supplementary appendix 3). A total of 60 participants completed enrollment and randomization, 32 (53%) were assigned to the sitagliptin and 28 (47%) were assigned to control (placebo) group. The clinical characteristics of study participants are shown in table 1. Groups were well matched at baseline, with no significant differences in age, gender, weight, body mass index, presence of comorbidities, type of surgery or American Society of Anesthesiologists status class (table 1). There were no differences in the mean glucose concentration at randomization (table 1), but those in the sitagliptin group had a slightly lower preoperative BG compared with placebo 101±18 mg/dL vs 107±13 mg/dL, p=0.013, respectively (table 2).

There were no differences in the primary endpoint, which was the frequency of stress hyperglycemia (BG

Table 1 Clinical characteristics on admission and glycemic control

	Placebo	Sitagliptin	P value
Participants (n)	28	32	
Gender			0.55
Male, n	23 (82)	24 (75)	
Age, years	64±9	64±11	0.75
Race			0.78
Caucasian	20 (71)	20 (63)	
African-American	6 (21)	9 (28)	
Other	2 (7)	3 (9)	
Body weight, kg	87±18	84±17	0.58
BMI, kg/m^2	28±6	28±6	0.77
Medical history			
Dyslipidemia	20 (74)	25 (78)	0.77
Hypertension	22 (79)	27 (84)	0.74
Previous cardiac intervention	10 (36)	14 (44)	0.60
Current smoker	9 (32)	6 (19)	0.37
Surgery			0.19
Elective/outpatient	10 (36)	19 (59)	
Emergent	1 (4)	2 (6)	
Transfer from another hospital	5 (18)	2 (6)	
Urgent	12 (43)	9 (28)	
Type of surgery			
Primary isolated CABG	23 (82)	25 (78)	0.76
CABG+valve repair	3 (11)	5 (16)	0.71
Previous CABG	3 (11)	2 (6)	0.65
Open CABG	24 (86)	27 (84)	>0.99
Robotic CABG	3 (11)	5 (16)	0.71
On pump	18 (75)	24 (89)	0.28
ASA			>0.99
III	5 (18)	6 (19)	
IV	23 (82)	25 (78)	
V	0	1 (3)	

Data are n (%); mean±SD.
ASA, American Society of Anesthesiologists; BMI, body mass index; CABG, coronary artery bypass graft surgery.

>180 mg/dL) during the operative period in participants treated with sitagliptin or placebo (38% vs 29%, p=0.59). We also explored differences in the proportion of participants with BG >140 mg/dL, which was also not significantly different between groups in all hospital settings (intraoperative: 75% vs 79%, ICU: 84% vs 82%, post-transition: 77% vs 69%, p=NS). While in the ICU, the number of participants who developed stress hyperglycemia (≥2 BG values >180 mg/dL) and required intravenous insulin therapy was similar in both groups (22% vs 25%, p>0.99). However, participants treated with sitagliptin required significantly lower total insulin dose during their first 48 hours in the ICU stay, compared with placebo (37±60 IU/day vs 83±64 IU/day, p=0.035)

Table 2 Glycemic control, insulin therapy and hospital complications

	Placebo	Sitagliptin	P value
Glycemic control			
Admission HbA1c, %	5.6±0.5	5.6±0.4	0.56
Randomization BG, mg/dL	106±13	100±18	0.17
Preoperative BG, mg/dL	107±13	101±18	0.013
BG during surgery, mg/dL	143±18	136±25	0.21
BG during ICU stay, mg/dL	138±25	137±16	0.78
BG after transition, mg/dL	124±16	123±13	0.75
Hyperglycemia BG >140 mg/dL (>7.8 mM)			
Participants with BG >140 mg/dL in OR	22 (79)	24 (75)	0.77
Participants with BG >140 mg/dL in ICU	23 (82)	27 (84)	>0.99
Participants with BG >140 mg/dL after transition	18 (69)	24 (77)	0.55
Hyperglycemia BG >180 mg/dL (>10.0 mM)			
Participants with BG >180 mg/dL in OR	8 (29)	12 (38)	0.59
Participants with >2 BG >180 mg/dL during CII	6 (21)	7 (22)	>0.99
Participants with BG >180 mg/dL after transition	8 (31)	8 (26)	0.77
Hyperglycemia BG >200 mg/dL (>11.1 mM)			
Participants with BG >200 mg/dL in OR	3 (11)	3 (9)	>0.99
Participants with BG >200 mg/dL in ICU	4 (14)	8 (25)	0.35
Participants with BG >200 mg/dL after transition	2 (8)	5 (16)	0.44
Hypoglycemia BG <70 mg/dL (<3.9 mM)			
Participants with hypoglycemia during ICU	1 (4)	2 (6)	>0.99
Participants with hypoglycemia after transition	0	1 (3)	>0.99
Hypoglycemia BG <40 mg/dL (<2.2 mM)			
Participants with BG <40 mg/dL (all settings)	0	0	–
Perioperative steroid administration	8 (29)	5 (16)	0.35
Number of BG readings in ICU	11.7±7.3	15.4±18.1	0.67
Number of BG readings after transition	20.4±8.5	20.0±11.2	0.51
Insulin therapy			
Participants treated with CII	7 (25)	7 (22)	>0.99
Duration of CII, hours	17 (9, 80)	12 (5, 88)	0.57
Total insulin dose in the ICU (first 48 hours), units	83±64	37±60	0.035
Participants treated with subcutaneous SSI after transition	5 (18)	5 (16)	>0.99
Subcutaneous insulin required, units	2.4±0.9	2.4±0.5	0.7
ICU LOS post-CABG, days (median)	2 (1, 3)	2 (1, 4)	0.82
Hospital LOS after randomization, days (median)	6.5 (4.5, 8.0)	6.0 (5.0, 9.0)	0.49
Complications during hospital admission			
Reintubation, n (%)	2 (7)	1 (3)	0.59
Readmission to ICU, n (%)	0	0	
Acute kidney injury, n (%)	2 (7)	5 (16)	0.43
Inotropes/vasopressor use >24 hours, n (%)	7 (25)	11 (34)	0.57
Myocardial infarction, n (%)	0	0	
Atrial fibrillation, n (%)	9 (32)	10 (31)	>0.99
Pulmonary edema, n (%)	4 (14)	4 (13)	>0.99
Heart failure, n (%)	2 (7)	2 (6)	>0.99
Stroke, n (%)	1 (4)	2 (6)	>0.99

Table 2 Continued

	Placebo	Sitagliptin	P value
Wound infection, n (%)	0	0	
Surgical site bleeding, n (%)	2 (7)	2 (6)	>0.99
Surgical reintervention, n (%)	2 (7)	1 (3)	0.59

Data are n (%), mean±SD, or median (IQR).
BG, blood glucose; CII, continuous insulin infusion; ICU, intensive care unit; LOS, length of stay; OR, operative room; SSI, sliding scale insulin.

(table 2). A small number of participants received steroids perioperatively (16% vs 29%, p=0.35) with no difference in glycemic control or insulin treatment. Both treatment groups had similar number of BG readings independent of the presence of hyperglycemia in the ICU or after transition to subcutaneous insulin (ICU readings: 15.4±18.1 vs 11.7±7.3; number of readings after transition: 20.0±11.2 vs 20.4±8.5, all p=NS).[39]

After the discontinuation of intravenous insulin and transition to subcutaneous insulin, the number of participants requiring subcutaneous insulin treatment was similar in both groups (16% vs 18%, p>0.99). The use of supplements or correctional insulin was also similar in both groups (2.4±0.5 IU/day in sitagliptin vs 2.4±0.9 IU/day in placebo, p=0.70) (table 2).

There were no differences in the mean BG during the operating room stay (136±25 mg/dL vs 143±18 mg/dL), ICU stay (137±16 mg/dL vs 138±25 mg/dL), or after transition (123±13 mg/dL vs 124±16 mg/dL) in the sitagliptin group compared with placebo (all p=NS). The duration of intravenous insulin infusion was 17 (IQR 9, 80) hours in the control group and 12 (IQR 5, 88) hours in the sitagliptin group (p=0.57). In addition, there were no differences in the rate of hypoglycemia or in mean daily glucose during the hospital stay between treatment groups.

Finally, we found no differences in the ICU or hospital LOS, duration of surgery, need for vasopressors, complications, surgical reinterventions or readmissions after hospital discharge between treatment groups. During the 30-day follow-up after hospital discharge, visits to the emergency room were similar in both groups (6% in the sitagliptin group vs 4% in the placebo, p>0.99) (table 3).

Table 3 Complication outcomes up to 30 days after hospital discharge

	Placebo	Sitagliptin	P value
Participants (n)	28	32	
Emergency room visits	1 (4)	2 (6)	>0.99
Readmissions due to wound infection	1 (4)	1 (3)	>0.99
Readmission due to other causes	0	3 (9)	0.24
Infections not requiring readmission	1 (4)	0 (0)	0.47

Data are n (%).

DISCUSSION

In this pilot, randomized, double-blinded, placebo-controlled trial, we explored whether the use of sitagliptin could prevent stress-induced hyperglycemia and the need for insulin treatment in patients without diabetes undergoing CABG. Our results indicate that the use of sitagliptin, starting before surgery and continued during the hospital stay, did not reduce the frequency of stress hyperglycemia compared with placebo (22% vs 21%, p>0.99) or the need for insulin therapy in the ICU or during the hospital stay.

The results of recent observational and randomized controlled studies have shown that the development of stress hyperglycemia after cardiac surgery is associated with higher rates of hospital complications, longer hospital stay, higher healthcare resource utilization, and a greater number of hospital complications.[18 19 40] As observed in this cohort, stress hyperglycemia (BG >140 mg/dL) after CABG surgery is reported in ~70% of patients without DM[1–3] and represents an independent risk factor of poor outcome compared with patients with normoglycemia[41] and in patients with known diabetes.[18 19] Despite ongoing debate about the optimal glucose target, there is strong agreement that improved glycemic control reduces perioperative complications in patients with DM[28 29 42] and with stress hyperglycemia.[43] Several studies have shown that treatment of stress hyperglycemia results in significant reductions of perioperative complications and mortality.[26 28 43] In the recent GLUCO-CABG trial[38] we reported that intensive insulin therapy to maintain a BG between 100 and 140 mg/dL in subjects without diabetes resulted in a significant reduction in perioperative complication compared with BG target between 141 and 180 mg/dL after CABG surgery. Similarly, a subgroup analysis by van den Berghe *et al*[43] of surgical ICU patients reported that intensive insulin therapy effectively reduced mortality in patients without a history of diabetes, but did not improve outcomes in patients with diabetes. These results suggest that the development of stress hyperglycemia is associated with poor outcomes in surgical patients and that improvement in glycemic control may reduce complications during the perioperative period. In this pilot study, the use of a DPP-4 inhibitor did not contribute to improving glycemic control in patients with stress hyperglycemia.

Clinical guidelines from professional organizations recommend the use of insulin to manage stress

hyperglycemia in cardiac surgery patients.[23 24 44] Although effective in improving glycemic control,[27–29] its use is labor intensive and is associated with higher risk of hypoglycemia.[30–33] Hypoglycemia after cardiac surgery, as hyperglycemia, has been found to be an independent factor for increased risk of complications, longer length of hospital stay, and increased mortality.[45–47] The increased risk of iatrogenic hypoglycemia with insulin therapy has triggered the search of alternative approaches and treatment regimens. Recently, several randomized controlled studies have reported that the treatment with DPP-4 inhibitors results in similar improvement in glycemic control than insulin therapy, but with lower risk of hypoglycemia, in non-critically ill hospitalized patients with type 2 diabetes and mild to moderate hyperglycemia.[34 48] Thus, we tested if stress hyperglycemia could be prevented with the use of a DPP-4 inhibitor, which could facilitate the management of patients after cardiac surgery. Unfortunately, our results indicate that treatment with sitagliptin was unsuccessful in preventing stress hyperglycemia after cardiac surgery. Among several causes, it could be possible that the time of administration of sitagliptin (24 hours prior to surgery) was not early enough to prevent stress hyperglycemia. One potential explanation could be that patients were kept NPO (Nil per Os) during the perioperative period. Native glucagon-like peptide-1 (GLP-1) is secreted in response to food intake, thus perhaps inhibition of the DPP-4 enzyme may not necessarily lead to a significant increase of circulating GLP-1 in these patients as compared with patients who are tolerating oral intake.[49] We could also speculate that the glycemic lowering effect of sitagliptin, an oral DPP-4 inhibitor, may not be potent enough to compensate for the stress hyperglycemic response. It is possible that the perioperative use of GLP-1 could achieve better glycemic control avoiding the need for insulin therapy after surgery.[44] We did observe lower insulin dose requirements and duration of insulin infusion among patients with hyperglycemia exposed to sitagliptin, which may shorten ICU stay for a patient and decrease the nursing effort spent on glycemic control.

We acknowledge several limitations in this trial, including the small number of randomized participants. This pilot study intended to generate preliminary estimates and to assess feasibility of a preoperative intervention to prevent stress hyperglycemia in patients without history of DM. We did observe minor differences in glucose levels before surgery and total insulin dose in the ICU among patients exposed to sitagliptin. These differences, however, are unlikely to be clinically significant. Our preliminary results do not justify the conduction of a larger clinical trial in patients without diabetes.

In summary, our findings indicate that the use of sitagliptin was well tolerated, but did not reduce the frequency of stress hyperglycemia or prevented the need for insulin therapy during the perioperative period after cardiac surgery.

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