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Original Article

Evaluation of the use of sitagliptin for insulin resistance in burn patients

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Abstract: Background: Following severe burn injury, patients undergo profound metabolic changes, including insulin resistance and hyperglycemia. Hyperglycemia has been linked to impaired wound healing, increased risk of skin graft loss, increased muscle catabolism, increased infections, and mortality. Sitagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor that improves glycemic control by slowing the inactivation of incretin hormones, increasing insulin synthesis and release from pancreatic beta cells and lowering glucagon secretion from pancreatic alpha cells. The objective of this study was to describe our institution's experience with using sitagliptin to help mitigate insulin resistance after burn injury. Methods: This was a retrospective chart review that included 22 adult burn patients. Burn patients were prescribed sitagliptin regardless of their previous medical history of type 2 diabetes mellitus. Patients were included in this analysis if they were adults admitted for burn injury during a 13-month period and received at least 3 consecutive doses of sitagliptin. Patients were excluded if they did not have insulin use data 3 days pre- and 3 days post-sitagliptin initiation. The first day of sitagliptin initiation was considered day 0; data from day 0 were not included in either the pre- or post-sitagliptin analysis. Results: In the 3 days prior to sitagliptin initiation, patients received a median of 114.3 units per day (IQR 49.1, 228) in an attempt to maintain a blood glucose goal of less than 180 mg/dL. In the 3 days after sitagliptin was started, exogenous insulin requirements significantly decreased to a median to 36.3 units per day (IQR 11.7, 95) (P=0.009). Seven patients were on insulin infusions at the time of sitagliptin initiation. After sitagliptin was started, it took a median of 3 days (IQR 2, 3.25) to be liberated from the insulin infusion. In terms of safety, there were two episodes of hypoglycemia (BG<70 mg/dL) after sitagliptin initiation, compared to three episodes prior to sitagliptin initiation (P=0.7). Conclusion: The addition of sitagliptin to burn patients' medication regimens significantly reduced insulin requirements over a 3-day period and allowed liberation from insulin drips.

Keywords: Insulin resistance, hyperglycemia, sitagliptin

Introduction

Metabolic changes following severe burn injury include inflammation, hypermetabolism, and hyperdynamic circulation. This physiologic stress, in turn, can lead to hyperglycemia and insulin resistance [1, 2]. Sustained increases in catecholamines, glucocorticoids, and glucagon occur. Catecholamines mediate glycogenolysis, thereby increasing blood glucose (BG) levels. Additionally, pro-inflammatory cytokines present after burn injury, including tumor necrosis factor (TNF), interleukin (IL)-6, and monocyte chemotactic protein-1 directly contribute to hyperglycemia by influencing skeletal muscle insulin resistance [2]. Critical illness adds another layer of complexity, causing shifts in metabolism that augment hepatic glucose production not suppressed by systemic hyperglycemia. Concurrently, glucose breakdown and disposal via the insulin-signaling pathway and glucose transporter-4 are inhibited, resulting in peripheral insulin resistance [2]. Sitagliptin works to improve glycemic control by slowing the inactivation of GLP-1 and GIP, increasing insulin synthesis and release from pancreatic beta cells and lowering glucagon secretion from pancreatic alpha cells [3]. This

increase in endogenous insulin production can potentially lower exogenous insulin requirements.

Persistent or sustained hyperglycemia has been associated with poor outcomes after burn injury, including increased risk of infection (pneumonia and bloodstream infections), augmented muscle catabolism, impaired wound healing, increased skin graft loss, and mortality [1, 2, 4, 5]. Additionally, achievement of intensive glycemic control has been associated with decreased incidence of pneumonia, including ventilator-associated pneumonia, and urinary tract infections [6]. Murphy and colleagues found that patients who did not achieve early glycemic control had a 6.75-fold increased risk of mortality even after adjusting for age, burn size, and presence of inhalation injury [4].

While the ideal BG target after burn injury has yet to be determined, current evidence indicates that BG should be maintained less than 180 mg/dL, with a goal of less than 150 mg/dL for trauma patients [7]. Some experts in managing burn injury and post-burn metabolic changes have suggested that the BG target should be lower in this patient population, with a goal less than 140 mg/dL or even less than 130 mg/dL [8, 9]. While intensive insulin therapy (targeting BG less than 110 mg/dL) has demonstrated increased survival and decreased infections in burn patients, these benefits must be carefully weighed against the risks of hypoglycemia [10, 11]. A recent study found that a standardized insulin protocol was able to achieve moderate glycemic control (targeting BG 110-140 mg/dL) in burn patients, while decreasing glucose variability and hypoglycemia [12].

Many burn patients require an insulin infusion to maintain BG levels within goal. For the past several years, in an effort to decrease insulin requirements and liberate patients from insulin infusions to facilitate transfer out of the burn intensive care unit (BICU), our center has utilized sitagliptin. Sitagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor that is currently indicated as an adjunctive treatment to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (DM) [3]. Sitagliptin improves glycemic control by slowing the inactivation of incretin hormones (glucagon-like peptide-1 [GLP-1] and glucose-dependent insulinotropic polypeptide [GIP]), thereby increasing insulin synthesis and release from pancreatic beta cells and lowering glucagon secretion from pancreatic alpha cells [3]. Based on its mechanism of action, sitagliptin can theoretically mitigate insulin resistance, decrease insulin requirements, and improve glycemic control both in patients with pre-existing type 2 DM and in patients without this diagnosis. Sitaglipin has been shown to have a minimal risk of hypoglycemia, making it an attractive adjunctive agent [3, 13].

The purpose of this study was to describe our clinical experience and evaluate our previous use of sitagliptin in patients admitted to our BICU, focusing on change in insulin requirements and ability to be liberated from insulin infusions.

Methods

This was a retrospective chart review was approved by the US Army Institute of Surgical Research's (USAISR) Research Regulatory Compliance Division as a performance improvement project (project number H-18-041nr). As this project was approved as a retrospective performance improvement project, informed consent was not required. All privacy and ethics standards were met. This project included all adult patients admitted to the burn intensive care unit (BICU) at the USAISR between June 1, 2017 and June 30, 2018. The primary endpoints included pre- and post-sitagliptin insulin requirements and time to liberation from insulin infusion. Safety endpoints included incidence of hypoglycemia (BG less than 70 mg/dL).

Patients were initiated on sitagliptin at the discretion of the BICU medical team if they were on an insulin infusion or needed more intensive BG monitoring and control, but were otherwise medically stable to be downgraded to ward-level care. Our institution utilizes a computerized decision support system (EndoTool®) for insulin infusion titration; a paper titration protocol is used in the event EndoTool® is unavailable. This system targets a BG less than 150 mg/dL. If for any reason Endotool® could not be used, a non-electronic insulin infusion titration protocol was used (**Appendix A**). Patients who

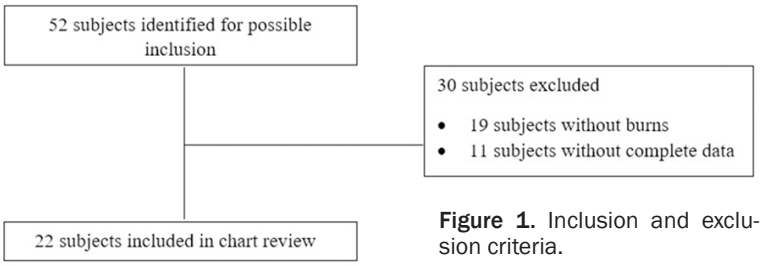

Figure 1. Inclusion and exclusion criteria.

were not on an insulin infusion were receiving sliding scale insulin every 6 hours (**Appendix B**).

Inclusion and exclusion criteria

Patients without burns (i.e. skin diseases, toxic epidermal necrolysis, necrotizing fasciitis) were excluded from this analysis. Patients were included if they received at least 3 consecutive doses of sitagliptin. Patients were excluded if they did not have insulin use data for the 3 days pre- and post-sitagliptin initiation. Patients who received sitagliptin were included regardless of their previous medical history of type 2 DM. Patients with a prior history of type 1 DM were not given sitagliptin, and therefore were not included in this chart review.

Data collection

The day of sitagliptin initiation was considered 'day 0'; data from this data were not included in our analysis. Data were collected from the electronic medical record and included demographic information, admission diagnosis, percent total body surface area burned (%TBSA), DM status, admission hemoglobin A_1C, creatinine clearance (CrCl, as per the Cockroft-Gault equation) at the time of sitagliptin initiation, dose of sitagliptin ordered, insulin requirements in the 3 days pre- and post-sitagliptin initiation, and time to insulin infusion discontinuation after sitagliptin was started. All subjects on enteral nutrition received our institution's standard formula of Promote® (Abbott Nutrition), which provides 25% of kcal from protein, 23% of kcal from fat, and 52% of kcal from carbohydrate. Diabetic enteral nutrition formulas were not used in our burn ICU. Carbohydrate intake data were recorded for each day, if available. When carbohydrate intake was not available, the analysis for carbohydrate intake pre- and post-sitagliptin was not used in the analysis for that patient.

Appropriate dosing was defined per the sitagliptin package insert. Patients with a CrCl, based on the Cockroft-Gault equation of 45 mL/min or higher, were recommended to receive sitagliptin 100 mg daily; patients with a CrCl of 30-44 mL/min were recommended to receive 50 mg daily; and patients with a CrCl of 29 mL/min or less were recommended to receive 25 mg daily [3].

Statistical analysis

Data were reported as mean ± standard deviation (SD) or median and interquartile range (IQR). Insulin requirements in the 72 hours pre-sitagliptin initiation and 72 hours post-sitagliptin initiation were compared and analyzed using a related-samples Wilcoxon signed rank test. Incidence of hypo- or hyperglycemia pre- and post-sitagliptin initiation was compared using Fisher's exact tests. Statistical significance was defined as an α-level of 0.05. Statistical analysis was performed using SPSS version 22 (IBM, Armonk, NY).

Results

Demographics

Fifty-two subjects were identified for possible inclusion, and 22 subjects were included in this analysis. **Figure 1** shows the number of patients included and excluded, along with reasons for exclusion. Demographic and baseline characteristics of these patients are included in **Table 1**. Ten (45.5%) patients had a formal diagnosis of type 2 DM and/or a hemoglobin A_1C value indicative of DM type 2 (≥6.5%) at hospital admission. Patients had an average burn size of 31.2% ± 23.2% TBSA, and 11 (50%) patients had inhalation injury. Sitagliptin was initiated a median of 22 days post-burn (IQR 11.5, 32 days). Adjusted for burn size, sitagliptin was initiated 0.8 days per %TBSA (IQR 0.5, 1.3 days per %TBSA) post-burn. The median duration of therapy was 10 days (IQR 7, 17 days).

Insulin requirements

In the 3 days prior to sitagliptin initiation, patients received a median of 114.3 units per

Table 1. Demographic characteristics

Characteristic	N=22
Age, years, mean ± SD	49.8 ± 19.9
Male gender, n (%)	17 (77.3)
BMI, kg/m^2, mean ± SD	32.2 ± 6.6
TBSA, %, mean ± SD	31.2 ± 23.2
Inhalation injury present, n (%)	11 (50)
Hemoglobin A_1C on admission, mean ± SD	6.5 ± 2
Diagnosis of type 2 DM prior to admission, n (%)	6 (27.3)
A_1C indicative of DM on admission, but without prior diagnosis of DM2 (≥6.5%), n (%)	4 (18.2)
Diabetics (A_1C indicative or prior diagnosis), n (%)	10 (45.5)
CrCl (Cockroft-Gault) when sitagliptin started, mean ± SD	155.9 ± 75.8
Renal replacement therapy when sitagliptin initiated, n (%)	2 (9.1)

Table 2. Insulin and carbohydrate intake (median, IQR)

	Pre-sitagliptin	Post-sitagliptin	*P*-value
Insulin requirement, units	114.3 (49.1, 228.1)	36.3 (11.7, 95)	0.009
Carbohydrates, g	1288.2 (910.8, 1643.3)	1326.5 (841.4, 1835.1)	0.613

day (IQR 49.1, 228.0) in an attempt to maintain a BG goal of less than 180 mg/dL. In the 3 days after sitagliptin was started, exogenous insulin requirements significantly decreased to a median of 36.3 units per day (IQR 11.7, 95.0) (P=0.031) (**Table 2**). **Figure 2** shows insulin requirements over time. Patients had a median 33.9% decrease in insulin requirements after starting sitagliptin (IQR-89.9, +9.9). The average enteral nutrition rate was 122 ± 43 mL/hr. The carbohydrate intake did not significantly differ before and after initiation of sitagliptin (1288.2 g vs. 1326.5 g; p=0.613) in the 17 patients who had carbohydrate intake data available (**Table 2**). Seven patients were on insulin infusions at the time of sitagliptin initiation. After sitagliptin was started, it took a median of 3 days (IQR 2.0, 3.3) to be liberated from the insulin infusion. The remaining patients had the insulin infusion discontinued on the day of or prior to sitagliptin initiation.

Blood glucose control

The median minimum BG was 99 (IQR 99, 121) mg/dL on day 1, 105 (IQR 89, 123) mg/dL on day 2, and 110 (IQR 90, 118) mg/dL on day 3. The median maximum BG was 202 (IQR 172, 240) mg/dL on day 1, 195 (IQR 163, 221) mg/dL on day 2, and 206 (IQR 149, 259) mg/dL on day 3. **Figure 3** shows the distribution of BG levels over the three days pre- and post-sitagliptin initiation. Twenty (90.9%) patients had at least one episode of hyperglycemia (BG> 180 mg/dL) prior to sitagliptin initiation, as compared to 17 (77.3%) patients after sitagliptin initiation (P=0.043).

Appropriate sitagliptin dosing

Fifteen patients (68.2%) were started an appropriate dose based on their renal function; 6 patients (27.3%) were started on too low of a dose, while 1 patient (4.5%) was started on too high of a dose. Four patients (18.2%) developed an acute kidney injury (AKI), defined as an increase in serum creatinine of ≥0.3 mg/dL per the AKIN criteria, during the first 3 days of sitagliptin therapy. Only one patient (4.5%) had an increase in serum creatinine >50% from the day of sitagliptin initiation to day 3 of sitagliptin therapy. The median change in serum creatinine from the day of initiation to day 3 of sitagliptin was an increase of 0.11 mg/dL (IQR -0.05, +0.09 mg/dL)).

Hypoglycemia

Prior to sitagliptin initiation, 3 patients (13.6%) had at least one episode of hypoglycemia. Two patients (9.1%) experienced hypoglycemia (BG<70 mg/dL) within the first 3 days after sitagliptin initiation; each patient only had 1 instance of hypoglycemia. One of these had pre-existing uncontrolled type 2 DM (admis-

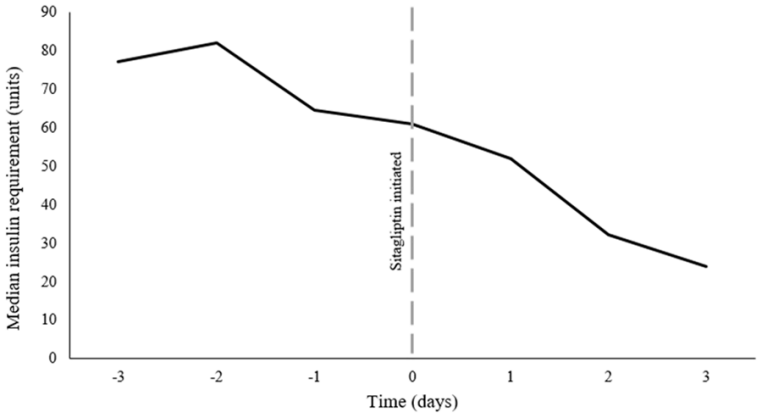

Figure 2. Insulin use over time.

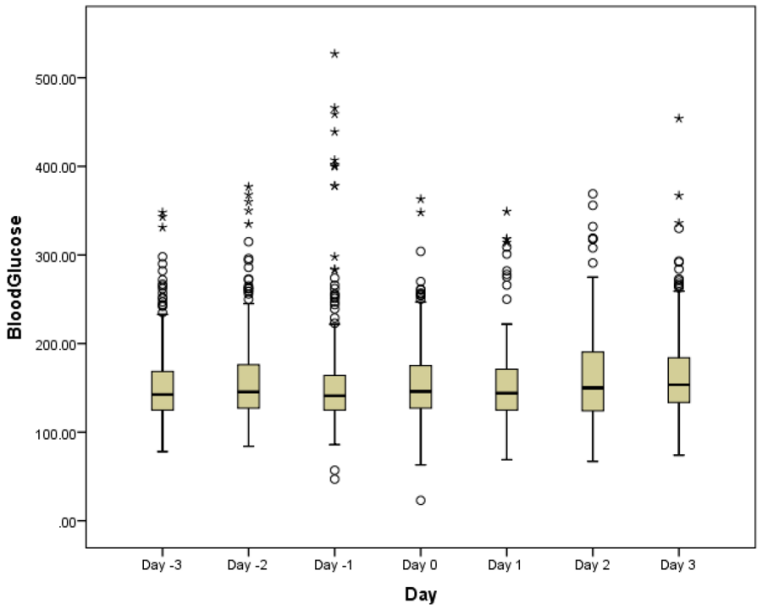

Figure 3. Blood glucose by day.

sion hemoglobin A1C was 11.4%). This patient had an average pre-sitagliptin insulin requirement of 124.7 units per day and a post-sitagliptin insulin requirement of 5.3 units per day. The other patient had an average requirement of 225 units per day and 2.7 units per day, respectively. Incidence of hypoglycemia was not significantly different pre- and post-sitagliptin initiation (13.6% vs. 9.1; P=0.7).

Discussion

We conducted a retrospective chart review to evaluate the use of sitagliptin as an adjunct anti-hyperglycemic agent post-burn injury. We found that the addition of sitagliptin was associated with decreased exogenous insulin requirements by an average of 33.9% in burn patients. Patients were able to be liberated from the insulin infusion and started on sliding-scale subcutaneous insulin an average of 3 days after sitagliptin initiation.

Hyperglycemia is a common metabolic consequence of burn injury. Exogenous insulin is the mainstay of therapy for treating hyperglycemia. To date, the only oral antidiabetic agent investigated to combat hyperglycemia after burn injury is metformin [14-16]. However, its potential for lactic acidosis precludes its use in most critically ill burn patients. We sought to explore the use of sitagliptin as an adjunct to insulin therapy for the management of hyperglycemia after burn injury.

In critically ill burn patients, it is important to achieve glycemic control, as this has been associated with decreased mortality and morbidity. Murphy and colleagues conducted a retrospective study, which showed that patients who failed to achieve early glycemic control (by post-burn day 3) had an increased risk of mortality [4]. In order to achieve early glycemic control, some burn experts recommend targeting a lower blood glucose level, as previously mentioned [1]. Lack of BG control has been associated with increased morbidity, Hyperglycemia has been associated with increased risk of morbidity, including pneumonia, bloodstream infections, and decreased graft take [17, 18].

While a BG level greater than 180 mg/dL should be avoided in critically ill burn/trauma patients, the ideal goal level remains unknown [5]. Studies examining the safety and efficacy

of intensive insulin therapy (targeting a BG level of 110 mg/dL or less) in burn patients have shown that intensive insulin therapy is associated with increased survival and decreased infections [10, 11]. In 2010, 73% of burn centers verified by the American Burn Association had insulin protocols that targeted BG levels less than 120 mg/dL [19]. An intensive insulin protocol implemented in a burn-trauma unit showed achievement of BG less than 120 mg/dL with only a 5% incidence of hypoglycemia per day [20]. However, intensive insulin therapy has been associated with increased risk of hypoglycemia in critically ill patient populations, with the risk of morbidity and mortality increasing with prolonged or frequent episodes of hypoglycemia [1, 2, 4, 5, 21].

The results from our study show that the addition of sitagliptin was associated with decreased episodes of hyperglycemia. In fact, 90.9% of patients had at least one episode of hyperglycemia (BG>180 mg/dL) prior to sitagliptin initiation, as compared to 77.3% of patients after sitagliptin initiation (P=0.043). Other studies in patients undergoing general and cardiac surgical procedures have not found the same results. It is estimated that 30% of non-diabetic patients undergoing non-cardiac procedures will develop stress hyperglycemia within 72 hours post-operatively. Fayfman and colleagues conducted a randomized pilot study to determine if sitagliptin could lower the risk of post-operative hyperglycemia in general surgery patients. Eighty patients were enrolled in this study; however, no significant differences in the rate of post-operative stress hyperglycemia, glycemic control, or complications were seen [22]. Brackbill and colleagues conducted a double-blind, placebo-controlled study to determine if there was a role for sitagliptin therapy for the acute control of BG management in the post-operative cardiac-surgery setting. They found that there was no difference in mean BG control between the sitagliptin and placebo groups, with both groups averaging about 150 mg/dL throughout the study period (P=0.388). Both groups required a mean of 13 units of insulin per day (P=0.942). Additionally, there was no difference in the incidence of post-operative infection, antibiotic use, and post-operative length of stay (LOS). In this study, there were 7 episodes of hypoglycemia (BG less than 60 mg/dL); 5 occurred in the sitagliptin group while 2 occurred in the placebo group [23]. Lastly, Cardona and colleagues conducted a double-blinded, placebo-controlled study to determine if sitagliptin could prevent stress hyperglycemia in patients undergoing coronary artery bypass surgery. While sitagliptin statistically significantly decreased BG levels pre-surgery, this was not clinically significant (101 mg/dL vs. 107 mg/dL; P=0.01). However, sitagliptin did not affect the proportion of patients who developed post-operative stress hyperglycemia (21% vs. 22%, P>0.99) [24]. In these studies, sitagliptin was initiated either on the day of or the day prior to surgery and may not have reached steady state during the study period. Additionally, both of these studies had a primary endpoint of BG levels, whereas daily insulin requirement was the primary endpoint in the present study.

To our knowledge, this is the first published report on sitagliptin in burn patients. However, there are several limitations to our study. This was a small, single-center, retrospective chart review, and carries inherent limitations due to the study design. Additionally, detailed carbohydrate data were not available for every patient on every day pre- or post-sitagliptin initiation; carbohydrate intake could have affected BG levels and insulin requirements. Lastly, other clinical data were not collected, such as the prevalence of infection/sepsis, time from burn injury, and percent total body surface area open. All of these factors have been associated with (or are anecdotally associated with) insulin resistance, exogenous insulin requirements, and BG levels.

Conclusion

The addition of sitagliptin to burn patients' medication regimens was associated with reduced exogenous insulin requirements over a 3-day period and allowed liberation from insulin drips. Larger studies are needed to validate these findings.

Disclosure of conflict of interest

The opinions or assertions contained herein are the private views of the authors, and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

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Appendix A. Insulin infusion titration protocol

INSULIN DRIP PAPER PROTOCOL

Two consecutive blood glucose levels >180mg/dL

- initiate insulin drip at 2 units/hr
- obtain blood glucose level every hour and select option below:

	Blood glucose value	Adjust insulin as follows:
Blood glucose level is <90 mg/dL	<70 mg/dL	turn drip off, give 12.5 gm D50W, recheck in 15 minutes
	70 - 90 mg/dL	turn drip off, recheck in 30 minutes

	Blood glucose decreases by:	Adjust insulin as follows:
Blood glucose level is DECREASING (but >90 mg/dL)	1-10 mg/dL in 1hr	Do not increase drip & do not give bolus
	11-25 mg/dL in 1hr	Decrease drip by 20% & do not give bolus
	26-50 mg/dL in 1hr	Decrease drip by 40% & do not give bolus
	51-75 mg/dL in 1hr	Decrease drip by 50% & do not give bolus
	76-100 mg/dL in 1hr	Decrease drip by 60% & do not give bolus
	>100 mg/dL in 1hr	Decrease drip by 70% & do not give bolus

	Blood glucose value:	Adjust insulin as follows:
Blood glucose level is INCREASING or SAME	91-100 mg/dL	Decrease drip by 2units/hr, no bolus
	101-125 mg/dL	Decrease drip by 1 unit/hr, no bolus
	126-150 mg/dL	No change in drip rate, no bolus
	151-175 mg/dL	Increase drip by 1unit/hr, no bolus
	176-200 mg/dL	Increase drip by 2 units/hr & give 2 unit bolus
	201-225 mg/dL	Increase drip by 2 units/hr & give 4 unit bolus
	226-250 mg/dL	Increase drip by 2 units/hr & give 6 unit bolus
	251-275 mg/dL	Increase drip by 2 units/hr & give 8 unit bolus
	276-300 mg/dL	Increase drip by 2 units/hr & give 10 unit bolus
	301-325 mg/dL	Increase drip by 2 units/hr & give 12 unit bolus
	326-350 mg/dL	Increase drip by 2 units/hr & give 14 unit bolus
	>350 mg/dL	Increase drip by 2 units/hr & give 16 unit bolus

**** IMPORTANT ****

- hold insulin drip when nutrition held
- restart insulin drip rate at previous rate when full nutrition is resumed
- notify MD when blood glucose <70 mg/dL or >250 mg/dL or insulin drip rate >25 units/hr

Appendix B. Sliding scale insulin protocol

	Blood Glucose	Units of Insulin Aspart
Very low dose	70-130 mg/dL	0 units
	131-180 mg/dL	1 unit
	181-240 mg/dL	2 units
	241-300 mg/dL	3 units
	301-350 mg/dL	4 units
	351-400 mg/dL	5 units
	>400 mg/dL	6 units and then call provider
Low dose	70-130 mg/dL	0 units
	131-180 mg/dL	2 units
	181-240 mg/dL	4 units
	241-300 mg/dL	6 units
	301-350 mg/dL	8 units
	351-400 mg/dL	10 units
	>400 mg/dL	12 units and then call provider
Moderate dose	70-130 mg/dL	0 units
	131-180 mg/dL	4 units
	181-240 mg/dL	6 units
	241-300 mg/dL	8 units
	301-350 mg/dL	10 units
	351-400 mg/dL	12 units
	>400 mg/dL	14 units and then call provider
High dose	70-130 mg/dL	0 units
	131-180 mg/dL	8 units
	181-240 mg/dL	12 units
	241-300 mg/dL	16 units
	301-350 mg/dL	20 units
	351-400 mg/dL	24 units
	>400 mg/dL	28 units and then call provider
Very high dose	70-130 mg/dL	0 units
	131-180 mg/dL	10 units
	181-240 mg/dL	14 units
	241-300 mg/dL	18 units
	301-350 mg/dL	22 units
	351-400 mg/dL	26 units
	>400 mg/dL	30 units and then call provider