ORIGINAL RESEARCH

Evaluation of Glycemic Control Following Discontinuation of an Intensive Insulin Protocol

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BACKGROUND: Intensive insulin protocols (IIPs) have been demonstrated to reduce morbidity and mortality in critically ill patients. Currently, there are no published studies evaluating glycemic control after discontinuation of an IIP.

OBJECTIVE: The purpose of this study was to compare blood glucose (BG) control during an IIP and for 5 days following its discontinuation (follow-up period).

METHODS: The study was a retrospective review of intensive care unit patients who received an IIP for $\geq$24 hours. Data were collected during the last 12 hours of the IIP and subsequent follow-up period.

RESULTS: For all 65 included patients, the mean $\pm$ standard deviation for BG on the IIP was 123 $\pm$ 26 mg/dL versus 168 $\pm$ 50 mg/dL following discontinuation of the IIP ($P < 0.001$). The median (interquartile range) insulin that was administered decreased from 40 (22–65) units on the IIP to 8 (0–18) units after the IIP was stopped ($P < 0.001$). The mean daily BG during the follow-up period was significantly higher than that during the IIP ($P < 0.001$). Additionally, an insulin requirement of >20 units during the last 12 hours of the IIP was identified as a risk factor for poor glycemic control during the follow-up period (odds ratio: 4.62; 95% confidence interval: 1.17–18.17).

CONCLUSIONS: This study demonstrates a significant increase in BG following discontinuation of an IIP. Higher insulin requirements during the last 12 hours of an IIP were identified as an independent risk factor for poor glycemic control following the IIP. A standardized insulin transition protocol may help better control BG after discontinuation of an IIP. ***Journal of Hospital Medicine*** **2009;4:28–34.**

KEYWORDS: intensive insulin, subcutaneous, transition.

Hyperglycemia and insulin resistance are common occurrences in critically ill patients, even those without a past medical history of diabetes.[1,2] This hyperglycemic state is associated with adverse outcomes, including severe infections, polyneuropathy, multiple-organ failure, and death.[3] Several studies have shown benefit in keeping patients' blood glucose (BG) tightly controlled.[3–7] In a randomized controlled study, strict BG control (80-110 mg/dL) with an insulin drip significantly reduced morbidity and mortality in critically ill patients.[3] A recent meta-analysis concluded that avoiding BG levels >150 mg/dL appeared to be crucial to reducing mortality in a mixed medical and surgical intensive care unit (ICU) population.[7]

The Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction study addressed the issue of tight glycemic control both acutely and chronically in 620 diabetic patients post–myocardial infarction. Patients were randomized to tight glycemic control (126-180 mg/dL) followed by a transition to

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maintenance insulin or to standard care. This intervention demonstrated a sustained mortality reduction of 7.5% at 1 year.[8] In contrast, the CREATE-ECLA study showed a neutral mortality benefit of a short-term (24-hour) insulin infusion in post–myocardial infarction patients.[9] These data demonstrate the need for clinicians to consider insulin requirements throughout the hospital stay and after discharge. To date, there are no published studies evaluating glycemic control following discontinuation of an intensive insulin protocol (IIP). Therefore, the current study was conducted to compare BG control during the use of an IIP and for the 5 days following intensive insulin therapy.

METHODS

Patient Population

This retrospective chart review was conducted at Methodist University Hospital (MUH), Memphis, TN. MUH is a 500-bed, university-affiliated tertiary referral hospital. The study was approved by the hospital institutional review board. From January 2006 to January 2007, a computer-generated pharmacy report was used to identify all patients receiving the hospital-approved IIP. Patients were included if they were $\geq$18 years old and received the IIP for $\geq$24 hours. Patients were excluded from the study if they met any of the following criteria: (1) complete BG measurements were not retrievable while the patient received the IIP or for the 5 days following discontinuation of the IIP, (2) the patient died while receiving the IIP, and (3) an endocrinologist was involved in the care of the patient.

IIP

The hospital-approved IIP is a paper-based, physician-initiated, nurse-managed protocol. Criteria required before initiating the IIP include (1) ICU admission, (2) 2 BG measurements >150 mg/dL, (3) administration of continuous exogenous glucose, and (4) absence of diabetic ketoacidosis. The goal range of the IIP is 80 to 150 mg/dL. Hourly BG measurements are initially required, but as control is achieved, measurements may be extended to every 2 hours and then every 4 hours. In general, the criteria used for transitioning off the IIP include stability during the last 12 hours. Patients were considered to be stable on the IIP if they had >70% of their glucose measurements within the goal range during the last 12 hours.

Data Collection

When inclusion criteria were met, patients' medical records were reviewed. Data collection included basic demographic information, concurrent medications, duration of IIP, amount of insulin administered during the last 12 hours of the IIP, insulin regimen post-IIP, and BG measurements during the last 12 hours on the IIP and for a total of 5 days after the IIP was stopped (follow-up period). For this study, hyperglycemia was defined as a BG value >150 mg/dL, significant hyperglycemia was defined as >200 mg/dL, and severe hyperglycemia was defined as >300 mg/dL. Hypoglycemia was defined as a BG value <60 mg/dL. The values of <60 mg/dL, >150 mg/dL, and >200 mg/dL were chosen on the basis of the criteria used in the MUH IIP and standard sliding-scale protocols. A value of >300 mg/dL was used to better describe patients with hyperglycemia. Poor glycemic control following the IIP was defined as a >30% change in mean BG during the last 12 hours on the drip and on the first day after discontinuation of the drip.

Statistical Analysis

The primary objective of this study was to compare BG control during the last 12 hours of an IIP and for the 5 days following its discontinuation. Secondary objectives were to evaluate the incidence of hyperglycemia and hypoglycemia during the transition period and to identify patients at risk of poor glycemic control following discontinuation of the IIP. Continuous data are appropriately reported as the mean $\pm$ standard deviation or median (interquartile range), depending on the distribution. Continuous variables were compared with the Student *t* test or Wilcoxon rank sum test. Discrete variables were compared with chi-square analysis and Bonferroni Correction where appropriate. For comparisons of BG during the IIP and on days 1 to 5 of the follow-up period, repeated-measures analysis of variance on ranks was conducted because of the distribution. These statistical analyses were performed with SigmaStat version 2.03 (Systat Software, Inc., Richmond, VA). A *P* value of less than 0.05 was considered significant. However, when the Bonferroni correction was used, a value of less than 0.01 was considered significant. Multivariable logistic regression was

TABLE 1
Patient Demographics and Insulin Requirements

	All Patients (n = 65)	PMH of DM (n = 36)	No PMH of DM (n = 29)
Age, mean years ± SD	62 ± 11	61 ± 10	64 ± 12
Male gender, n (%)	38 (58)	22 (61)	16 (55.2)
BMI ± SD	30 ± 7.2	31 ± 7	30 ± 6.5
Surgery, n (%)	49 (74.2)	27 (75)	21 (72.4)
CABG, n	38	22	16
Liver transplant, n	6	1	4
Other, n	5	4	1
Last 24 hours on IIP, n (%)			
Ventilator	37 (56.9)	22 (61.1)	15 (51.7)
Antibiotics	37 (56.9)	20 (55.6)	17 (58.6)
Vasopressors	11 (16.9)	5 (13.9)	6 (20.7)
Hemodialysis	8 (12.3)	5 (13.9)	3 (10.3)
Steroids	16 (24.6)	9 (25)	7 (24.1)
Duration of IIP, mean hours ± SD	72 ± 65	80 ± 78	62 ± 45
Insulin during last 12 hours of IIP, mean units ± SD	47 ± 37	51 ± 30	46 ± 45
Type of insulin received following IIP, n (%)			
Scheduled + sliding scale	25 (38.5)	19 (52.8)	6 (20.7)
Sliding scale only	38 (58.5)	16 (44.4)	22 (75.9)
None	2 (3)	1 (2.8)	1 (3.4)
Total daily insulin following IIP, mean units ± SD	28 ± 41	38 ± 49	17 ± 24
Patients stable on IIP	44 (67.7)	23 (64.8)	21 (72.4)
Hospital LOS, mean days ± SD	24 ± 18	24 ± 17	23 ± 19
Mortality, n (%)	15 (23.1)	5 (13.8)	10 (34.5)

Abbreviations: BMI, body mass index; CABG, coronary artery bypass graft; DM, diabetes mellitus; IIP, intensive insulin protocol; LOS, length of stay; PMH, past medical history; SD, standard deviation.

used to determine independent predictors of a greater than 30% change in the mean BG value between the last 12 hours of the IIP and the first day off the insulin drip. Potential independent variables included in the analysis were stability on protocol, requiring less than 20 units of insulin in the last 12 hours on the IIP, use of antibiotics, use of steroids, history of diabetes, and type of insulin to which the patient was transitioned (none, sliding scale, and scheduled and sliding scale). The model was built in a backwards, stepwise fashion with SAS version 9.1 (SAS Institute, Cary, NC).

RESULTS

A total of 171 patients received the IIP during the study period. Ninety-seven patients did not meet inclusion criteria because they received the IIP for less than 24 hours. Of the 74 patients meeting inclusion criteria, 9 were excluded (5 had insufficient glucose data, 3 were cared for by an endocrinologist, and 1 died while receiving the IIP). Thus, 65 patients were included in the study.

Table 1 lists the baseline demographics for all patients and those with and without a history of diabetes mellitus (DM). The majority of the patients (n = 49) underwent a surgical procedure, with the most common procedure being coronary artery bypass graft (n = 38). Patients undergoing coronary artery bypass graft had the IIP included in their standard postoperative order set. The majority of patients were considered stable during the 12 hours prior to discontinuation of the IIP, including 23 patients with a history of DM. Of the 65 patients who were included in the study, 25 (38.5%) received a scheduled insulin order following discontinuation of the IIP, whereas 38 (58.5%) received some form of sliding-scale insulin (SSI). Additionally, 2 (3%) patients did not receive any form of insulin order after stopping the IIP. Of those receiving scheduled insulin, 15 (60%) received neutral protamine Hagedorn, 5 (20%) received glargine, 5 (20%) received 70/30, and 1 (4%) received regular insulin. Of those receiving SSI only, the prescribed frequency was as follows: every 4 hours for 17 (45%), before meals and at

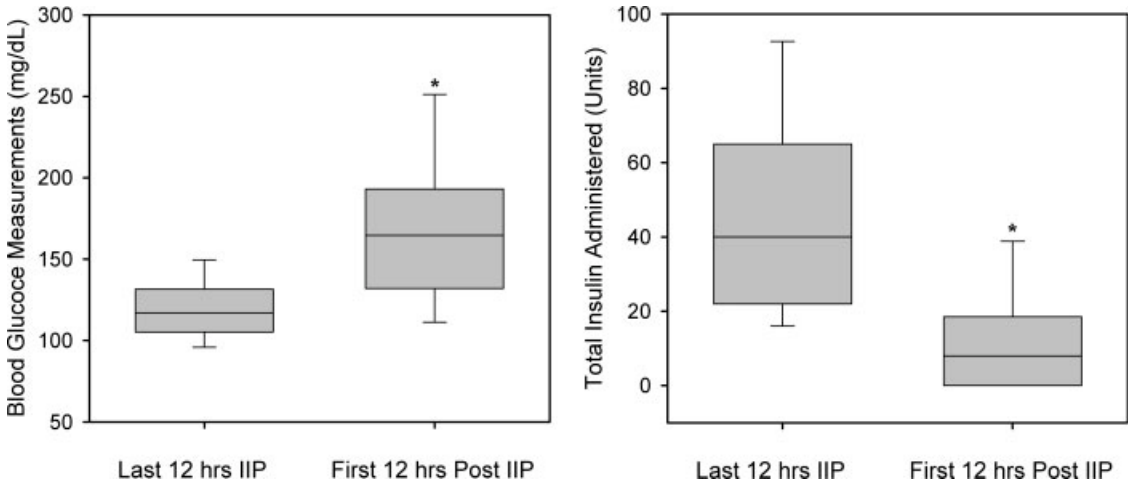

FIGURE 1. Blood glucose measurements and insulin requirements during the last 12 hours of the intensive insulin protocol (IIP) and the first 12 hours following the IIP. *$P < 0.001$. Boxes represent interquartile ranges; whiskers represent 10th and 90th percentiles.

bedtime for 15 (39%), every 6 hours for 5 (13%), and every 2 hours for 1 (3%).

A total of 562 glucose measurements were collected during the last 12 hours on the IIP, whereas 201 were collected during the first 12 hours immediately following the IIP. Patients demonstrated a significant increase in BG (mean ± standard deviation) during the first 12 hours of the follow-up period versus the last 12 hours of the IIP (168 ± 50 mg/dL versus 123 ± 26 mg/dL, $P < 0.001$). This corresponded to a significant decrease in the median (interquartile range) insulin administered during the first 12 hours of the follow-up period versus the last 12 hours of the IIP [8 (0-18) units versus 40 (22-65) units, $P < 0.001$; Figure 1]. A total of 1914 BG measurements were collected during the follow-up period. Figure 2 shows mean BG values for all patients on the IIP compared to mean BG values for each day of the follow-up period. There was a significant increase in mean BG measurements when the IIP was compared to each day of the follow-up period, but there was no difference between days of the follow-up period. Table 2 shows the proportion of patients experiencing at least 1 episode of hyperglycemia (BG > 150 mg/dL), significant hyperglycemia (BG > 200 mg/dL), severe hyperglycemia (BG > 300 mg/dL), or hypoglycemia (BG < 60 mg/dL) while receiving the IIP and during the follow-up period. When comparing the IIP to the follow-up period, we found a significant increase in the proportion of patients with at least 1 BG > 150 mg/dL. This was also true for patients with a BG of > 200 mg/dL.

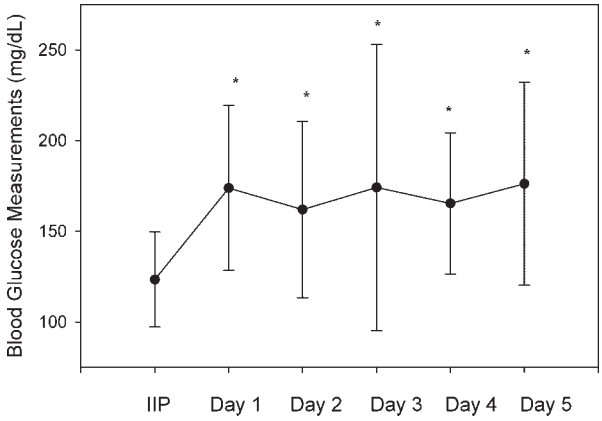

FIGURE 2. Blood glucose measurements during the intensive insulin protocol (IIP) and on days 1 to 5 following discontinuation of the IIP. *On the basis of analysis of variance with a pairwise multiple comparison procedure (Tukey test), blood glucose values (mean ± standard deviation) were significantly lower on the IIP (123 ± 26 mg/dL) than on day 1 (174 ± 45 mg/dL, $P < 0.001$), day 2 (162 ± 49 mg/dL, $P < 0.001$), day 3 (174 ± 79 mg/dL, $P < 0.001$), day 4 (165 ± 39 mg/dL, $P < 0.001$), or day 5 (177 ± 56 mg/dL, $P < 0.001$).

The only independent predictor of a greater than 30% change in mean BG was the requirement for more than 20 units of insulin (>1.7 units/hour) during the last 12 hours on the IIP.

TABLE 2
Proportions of Patients with at Least 1 Episode of Hyperglycemia or Hypoglycemia

	IIP (n = 65)	Day 1 (n = 65)	Day 2 (n = 65)	Day 3 (n = 64)	Day 4 (n = 62)	Day 5 (n = 59)
Patients with >150 mg/dL, n (%)	33 (51)	54 (83)*	54 (83)*	52 (81)*	51 (82)*	48 (81)*
Patients with >200 mg/dL, n (%)	11 (17)	37 (57)*	31 (48)*	26 (41)*	33 (53)*	34 (58)*
Patients with >300 mg/dL, n (%)	2 (3)	11 (17)	7 (11)	8 (12)	5 (8)	10 (17)
Patients with <60 mg/dL, n (%)	6 (9)	5 (8)	2 (3)	2 (3)	2 (3)	0 (0)

Abbreviation: IIP, intensive insulin protocol.
*Based on chi-square analysis with Bonferroni correction ($P < 0.001$).

The odds of a greater than 30% change was 4.62 times higher (95% confidence interval: 1.17–18.17) in patients requiring more than 20 units during the last 12 hours on IIP after adjustments for stability on the protocol and past medical history of diabetes. Stability on the protocol was not identified as an independent predictor, with an adjusted odds ratio of 2.40 (95% confidence interval: 0.79–7.32).

DISCUSSION

This is the first study to describe glycemic control following the transition from an IIP to subcutaneous insulin. We observed that during the 5 days following discontinuation of an IIP, patients had significantly elevated mean BG values. These data are highlighted by the fact that patients received significantly less insulin during the first 12 hours of the follow-up period versus the last 12 hours of the IIP. Additionally, a larger than expected proportion of patients exhibited at least 1 episode of hyperglycemia during the follow-up period. We also found that an increased insulin requirement of >1.7 units/hour during the last 12 hours of the IIP was an independent risk factor for a greater than 30% increase in mean BG on day 1 of the follow-up period.

Increasing evidence demonstrates that the development of hyperglycemia in the hospital setting is a marker of poor clinical outcome and mortality. In fact, hyperglycemia has been associated with prolonged hospital stay, infection, disability after discharge, and death in patients on general surgical and medical wards.[10–12] This makes the increase in mean BG found in our study following discontinuation of the IIP a concern.

SSI with subcutaneous short-acting insulin has been used for inpatients as the standard of care for many years. However, evidence supporting the effectiveness of SSI alone is lacking, and it is not recommended by the American Diabetes Association.[13] Queale et al.[14] showed that SSI regimens when used alone were associated with suboptimal glycemic control and a 3-fold higher risk of hyperglycemic episodes.[1] Two retrospective studies have also demonstrated that SSI is less effective and widely variable in comparison with proactive preventative therapy.[15,16] In the current study, 58.5% of patients received SSI alone during the follow-up period. As indicated in Figure 1, there was a significant increase in mean BG during this time interval. The choice of an inappropriate insulin regimen might be a contributing factor to poor glycemic control.

Because only 38.5% of patients were transitioned to scheduled insulin in our study, one possible strategy to help improve glycemic control would be to transition patients to a scheduled insulin regimen. Umpierrez et al.[12] conducted a prospective, multicenter randomized trial to compare the efficacy and safety of a basal-bolus insulin regimen with that of SSI in hospitalized type 2 diabetics. These authors found that patients treated with insulin glargine and glulisine had greater improvement in glycemic control than those treated with SSI ($P < 0.01$).[12] Interestingly, the basal-bolus method provides a maintenance insulin regimen that is aggressively titrated upward as well as an adjustable SSI based on insulin sensitivity. Patients in the current study may have benefited from a similar approach as many did not have their scheduled insulin adjusted despite persistent hyperglycemia.

With the increasing evidence for tight glycemic control in the ICU, a standardized transition from an intensive insulin infusion to a subcutaneous basal-bolus regimen or other scheduled regimen is needed. To date, the current study is the first to describe this transition. Based on these

data, recommendations for transitioning patients off an IIP provided by Furnary and Braithwaite[17] should be considered by clinicians. In fact, one of their proposed predictors for unsuccessful transition was an insulin requirement of $\geq$2 units/hour. Indeed, the only independent risk factor for poor glycemic control identified in the current study was a requirement of >20 units (>1.7 units/hour) during the last 12 hours of the IIP. Further research is required to verify the other predictors suggested by Furnary and Braithwaite. They recommended using a standardized conversion protocol to transition patients off an IIP.

More recently, Kitabchi et al.[18] recommended that a BG target of less than 180 mg/dL be maintained for the hospitalized patient.[18] Although our study showed a mean BG less than 180 mg/dL during the follow-up period, the variability in these values raises concerns for individual patients.

The current study is limited by its size and retrospective nature. As with all retrospective studies, the inability to control the implementation and discontinuation of the IIP may confound the results. However, this study demonstrates a real world experience with an IIP and illustrates the difficulties with transitioning patients to a subcutaneous regimen. BG values and administered insulin were collected only for the last 12 hours on the IIP. This duration is considered appropriate as this time period is used clinically at MUH, and previous recommendations for transitioning patients suggest using a time period of 6 to 8 hours to guide the transition insulin regimen.[17] In addition, data regarding the severity of illness and new onset of infections were not collected for patients in the study. Both could affect glucose control. All patients had to be in an ICU to receive the IIP, but their location during the follow-up period varied. Although these data were not available, control of BG is a problem that should be addressed whether the patient is in the ICU or not. Another possible limitation of the study was the identification of patients with or without a past medical history of DM. The inability to identify new-onset or previously undiagnosed DM may have affected analyses based on this variable.

CONCLUSIONS

This study demonstrated a significant increase in mean BG following discontinuation of an IIP; this corresponded to a significant decrease in the amount of insulin administered. This increase was sustained for a period of at least 5 days. Additionally, an independent risk factor for poor glycemic control immediately following discontinuation of an IIP was an insulin requirement of >1.7 units/hour during the previous 12 hours. Further study into transitioning off an IIP is warranted.

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REFERENCES

1. McCowen KC, Malthora A, Bistrian BR. Stress-induced hyperglycemia. *Crit Care Clin*. 2001;17:107–124.
2. Mizock BA. Alterations in carbohydrate metabolism during stress: a review of the literature. *Am J Med*. 1995;98:75–84.
3. Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med*. 2001; 345:1359–1367.
4. Krinsley JS. Effect of an intensive glucose management protocol on the mortality of critically ill adult patients. *Mayo Clin Proc*. 2004;79(8):992–1000.
5. Van den Berghe G, Wilmer A, Hermans G, et al. Intensive insulin therapy in the medical ICU. *N Engl J Med*. 2006; 354:449–461.
6. Malmberg K, Ryden L, Wedel H, et al. Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2) effects on mortality and morbidity. *Eur Heart J*. 2005;26:651–661.
7. Van den Berghe G, Wilmer A, Milants I, et al. Intensive insulin therapy in mixed medical/surgical intensive care units. *Diabetes*. 2006;55:3151–3159.
8. Malmberg K, Ryden L, Hamsten A, et al. Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): effects on mortality at 1 year. *J Am Coll Cardiol*. 1995;26:56–65.
9. Mehta SR, Yusuf S, Diaz R, et al. Effect of glucose-insulin-potassium infusion on mortality in patients with acute ST-segment elevation myocardial infarction: the CREATE-ECLA randomized controlled trial. *JAMA*. 2005;293(4): 437–446.
10. Umpierrez GE, Isaacs SD, Bazargan N, You X, Thaler LM, Kitabchi AE. Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. *J Clin Endocrinol Metab*. 2002;87:978–982.
11. Clement S, Braithwaite SS, Magee MF, et al. Management of diabetes and hyperglycemia in hospitals. *Diabetes Care*. 2004;27:553–597.
12. Umpierrez GE, Smiley D, Zisman A, et al. Randomized study of basal-bolus insulin therapy in the inpatient management of patients with type 2 diabetes (RABBIT 2 trial). *Diabetes Care*. 2007;30(9):2181–2186.

13. Fonseca V, Bakris GL, Benjamin EA, et al., for the American Diabetes Association Professional Practice Committee. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2006;29(suppl 1):43–48.
14. Queale WS, Seidler AJ, Brancati FL. Glycemic control and sliding scale insulin use in medical inpatients with diabetes mellitus. *Arch Intern Med*. 1997;157(5):545–552.
15. Golightly LK, Jones MA, Hamamura DH, Stolpman NM, McDermott MT. Management of diabetes mellitus in hospitalized patients: efficiency and effectiveness of sliding-scale insulin therapy. *Pharmacotherapy*. 2006;26(10):1421–1432.
16. Gearhart JG, Duncan JL III, Replogle WH, Forbes RC, Walley EJ. Efficacy of sliding-scale insulin therapy: a comparison with prospective regimens. *Fam Pract Res J*. 1994;14(4):313–322.
17. Furnary AP, Braithwaite SS. Effects of outcome on in-hospital transition from intravenous insulin infusion to subcutaneous therapy. *Am J Cardiol*. 2006;98:557–564.
18. Kitabchi AE, Freire AX, Umpierrez GE. Evidence for strict inpatient blood glucose control: time to revise glycemic goals in hospitalized patients. *Metabolism*. 2008;57:116–120.