

Is Incretin-Based Therapy Ready for the Care of Hospitalized Patients With Type 2 Diabetes?

The time has come for GLP-1 receptor agonists!

Significant data suggest that overt hyperglycemia, either observed with or without a prior diagnosis of diabetes, contributes to an increase in mortality and morbidity in hospitalized patients. In this regard, goal-directed insulin therapy has remained as the standard of care for achieving and maintaining glycemic control in hospitalized patients with critical and noncritical illness. As such, protocols to assist in the management of hyperglycemia in the inpatient setting have become commonplace in hospital settings. Clearly, insulin is a known entity, has been in clinical use for almost a century, and is effective. However, there are limitations to its use. Based on the observed mechanisms of action and efficacy, there has been a great interest in using incretin-based therapy with glucagon-like peptide-1 (GLP-1) receptor agonists instead of, or complementary to, an insulin-based approach to improve glycemic control in hospitalized, severely ill diabetic patients. To provide an understanding of both sides of the argument, we provide a discussion of this topic as part of this two-part point-counterpoint narrative. In this point narrative as presented below, Drs. Schwartz and DeFronzo provide an opinion that now is the time to consider GLP-1 receptor agonists as a logical consideration for inpatient glycemic control. It is important to note the recommendations they propose under “incretin-based approach” with these agents represent their opinion for use and, as they point out, well-designed prospective studies comparing these agents with insulin will be required to establish their efficacy and safety. In the counterpoint narrative following Drs. Schwartz and DeFronzo’s contribution, Drs. Umptierrez and Korytkowski provide a defense of insulin in the inpatient setting as the unquestioned gold standard for glycemic management in hospitalized settings.

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Controversy exists concerning the role of intensified glycemic control in critically ill, hospitalized diabetic patients (1,2). Results with insulin therapy largely have been disappointing. In the current point-counterpoint debate, we advocate and provide evidence to support the use of glucagon-like peptide-1 (GLP-1) analogs because of their ability to control stress-induced hyperglycemia with minimal side effects, especially hypoglycemia.

Poor glycemic control predicts increased mortality in hospitalized patients—In noncritically ill medical/surgical patients and in patients in intensive care units, hyperglycemia is frequent, occurring in >30–50% of individuals (3,4). Hyperglycemia is an independent risk marker of in-hospital mortality in patients with undiagnosed diabetes and in individuals without diabetes (4,5), and even mild glucose elevations (fasting plasma glucose >110 mg/dL) are associated with increased (threefold)

mortality in patients undergoing percutaneous coronary intervention (5). Because hyperglycemia is a predictor of adverse outcome, it logically follows that hospitalized patients would benefit from improved glycemic control.

Insulin therapy fails to reduce mortality—In hyperglycemic patients hospitalized for acute myocardial infarction (MI) (6,7) and in the surgical intensive care unit (ICU) (8) and burned pediatric ICU (9) patients, improved glycemic control with insulin has been shown to be associated with reduced mortality in some studies. However, most studies in ICU patients have failed to demonstrate any benefit on mortality with intensive insulin therapy (10–12), and two large randomized trials (13,14) with insulin in ICU patients were stopped prematurely because of increased hypoglycemia and lack of benefit. Hypoglycemia is a serious complication of insulin therapy and has been shown to be associated with negative outcomes (15).

Hypoglycemia exerts many deleterious effects on the cardiovascular system including 1) prolonged QT interval, which lasts for an extended period and 2) stimulation of catecholamine release, which can precipitate angina, cause electrocardiogram abnormalities, and ischemic electrocardiogram changes, induce arrhythmias, and cause sudden death.

Incretin therapy has multiple benefits over insulin in the management of critically ill, hospitalized patients

—GLP-1 receptor analogs exert a number of metabolic effects that make them attractive agents for the treatment of hyperglycemia in critically ill, hospitalized patients including 1) glucose-dependent stimulation of insulin secretion (16), thereby preventing hypoglycemia (15); 2) inhibition of glucagon secretion; 3) suppression of hepatic glucose production secondary to enhanced insulin secretion and inhibition of glucagon secretion; 4) enhanced tissue sensitivity to insulin (17,18); 5) beneficial effects on cardiovascular risk factors (reduced systolic/diastolic blood pressure, triglycerides, LDL cholesterol, high-sensitivity C-reactive protein, B-type natriuretic peptide, inflammatory cytokines, and oxidative stress); and 6) improved cardiovascular and endothelial function (19) (Table 1). Further, in preclinical studies GLP-1 has been shown to reduce infarct size (reviewed in reference 20).

In contrast, in critically ill, hospitalized patients insulin therapy is associated with an unacceptably high incidence of hypoglycemia (11,14,15), aggravates the underlying insulin resistance (21), may adversely affect cardiovascular risk factors and endothelial function (22,23), does not reduce cardiovascular events (23–25), and most importantly does not improve mortality (11–14). In contrast, meta-analysis of patients in the exenatide database showed a hazard ratio for cardiovascular events of 0.69 (95% CI 0.46–1.04) (26).

Table 1—Benefits/risks of GLP-1 receptor agonist and insulin therapy

	GLP-1 receptor agonists	Insulin
Glycemic control	Very good	Very good
Hypoglycemia	Minimal	Significant
Improved mortality and cardiovascular outcomes	To be determined	Controversial, many negative studies
Specifically counteracts stress-induced hyperglycemia	Yes	No
Gastrointestinal side effects	Small	None
Therapeutic approach	Simple, little dose titration can obviate need for insulin	Complicated, requires significant dose titration

Cardiovascular benefits of incretin hormones

—Recent reviews (20) have examined the cardiovascular benefits of incretin therapy including enhanced cardiac myocyte viability after ischemic injury, increased systolic function in preclinical models and humans, coronary arterial vasodilatation, improved endothelial function, increased sodium excretion, and protection of neural cells against hyperglycemic injury. Both exenatide and liraglutide exert these effects.

A 72-h GLP-1 infusion in acute MI patients with and without diabetes significantly improved left ventricular ejection fraction (27). Improved left ventricular function also has been observed in congestive heart failure patients who received a 5-week GLP-1 infusion following acute MI (28). GLP-1 infusion has been shown to improve myocardial functional recovery in the peri-infarct zone following an MI (28) and in patients undergoing coronary artery bypass graft surgery (27,29). GLP-1 therapy reduced the need for vasopressors, decreased the incidence of arrhythmias, and improved glycemic control in the pre- and perioperative periods (95 vs. 140 mg/dL, $P < 0.02$) despite 45% less insulin compared with the control group (29). Similar results after cardiac surgery have been reported by others (30).

β -Cell function, incretins, and stress diabetes

—In response to stress, the body releases counter-regulatory hormones (cortisol, glucagon, catecholamines, growth hormone) that cause insulin resistance in muscle and stimulate hepatic glucose production (31). Catecholamines also impair insulin secretion via α -adrenergic receptor activation, while glucocorticoids exert a potent inhibitory

effect on insulin secretion and augment glucagon secretion (32,33). Glucocorticoids also induce β -cell apoptosis, an effect that requires expression of Pdx-1 and can be prevented by GLP-1 (34). Importantly, these stress-induced hormones act synergistically to raise the blood glucose concentration (31,35).

Hyperglucagonemia commonly is observed in the postsurgical setting and in critically ill patients (36) and causes glucose intolerance by stimulating hepatic glucose production (37). Further, physiologic hyperglucagonemia for as little as 3 days causes severe insulin resistance in peripheral (muscle) tissues (37). GLP-1 is a potent inhibitor of glucagon secretion and reduces elevated plasma glucagon levels (17) that occur in postsurgical patients. GLP-1 analogs also counteract the negative effect of steroids on insulin secretion and prevent the development of hyperglycemia (32).

After major surgery in type 2 diabetic patients, intravenous GLP-1 has been shown to normalize blood glucose levels in association with increased insulin and reduced plasma glucagon concentrations without causing hypoglycemia (38). When administered post-coronary artery bypass surgery, GLP-1 was as effective as insulin in normalizing blood glucose without causing hypoglycemia (30) and reduced glucose levels from 162 to 124 mg/dL following angioplasty in patients with acute MI (28). In type 2 diabetic patients undergoing coronary artery bypass surgery (30), GLP-1 infusion decreased the amount of insulin required to achieve glycemic control. Importantly, gastrointestinal side effects, nausea, and vomiting have not been a problem in the studies described above. In the studies by Müssig et al. (30) and Sokos et al. (29), no nausea was observed in any patient.

GLP-1 receptor agonists in the intensive care setting

—The use of GLP-1 analogs in treating critically ill patients in medical/surgical ICUs is of great interest because they can restore normoglycemia without causing hypoglycemia and have potential cardiovascular benefit (20). In a preliminary study, Marso et al. (39) reported excellent results with intravenous exenatide (bolus = 0.05 μ g/min for 30 min followed by 0.025 μ g/min) in 40 adults admitted to the cardiac ICU. It took 3.9 h to reduce and maintain plasma glucose from 199 to 140 mg/dL for the subsequent 48 h. Blood glucose levels <70 mg/dL were uncommon. We (S.S.) have administered placebo ($n = 10$), low-dose exenatide (0.27 ng/kg \cdot min), and high-dose exenatide (0.41 0.27 ng/kg \cdot min) intravenously during cardiac ($n = 12$) and noncardiac ($n = 18$) surgical procedures in diabetic and nondiabetic patients with normalization of blood glucose levels and decreased glycemic excursions (40). At 150 min after the start of surgery, the median blood glucose was 187, 144, and 141 mg/dL in subjects treated with placebo, low-dose exenatide, and high-dose exenatide, respectively. There were no episodes of hypoglycemia or adverse effects in any group. Twice-daily subcutaneous administration of exenatide has been studied in severely burned patients, and a significant reduction in insulin requirement with earlier withdrawal of insulin therapy has been observed (41).

Many critically ill patients require insulin, often in large doses, to restore normoglycemia. GLP-1 analogs safely can be combined with insulin. Since diabetic—as well as nondiabetic—critically ill patients often require insulin, the use of incretins and insulin may need to be combined. Garber et al. (42) have estimated that 85% of in-hospital patient hypoglycemia is because of bolus insulin therapy and 15% because of basal insulin therapy. It is the authors' experience that by combining a GLP-1 analog with basal insulin, the need for bolus insulin therapy can be largely obviated, thereby markedly reducing the incidence of hypoglycemia.

In-hospital treatment of type 2 diabetes

Screening for diabetes and hyperglycemia

Hyperglycemia is an independent risk factor for all-cause mortality in critically ill, hospitalized medical and surgical

patients (5,6). Insulin currently represents the standard of care for seriously ill patients in the perioperative period, in ICUs, and on general medical/surgical wards (1). From a theoretical standpoint, one would expect tight glycemic control to improve outcomes in these critically ill patients. However, the American College of Physicians has recommended avoiding *intensive* insulin therapy in critically ill patients (2) because recent studies have failed to show benefit on morbidity or mortality (11–14) and have demonstrated an increased incidence of side effects, especially hypoglycemia (15). It is possible that the underlying disease process is so severe that it obscured the benefit of intensified glycemic control with insulin in these severely ill patients. Alternatively, side effects associated with intensified insulin therapy could have offset any potential benefit on morbidity/mortality. The risks associated with insulin-induced hypoglycemia are well documented and include sympathetic nervous system activation, increased stroke volume and myocardial oxygen consumption, arrhythmias, hypokalemia, and hypophosphatemia. Approaches to reduce the frequency and severity of these side effects have been developed (43). Nonetheless, the incidence of side effects with insulin therapy, especially hypoglycemia, remains high and presents a barrier to achieving tight glycemic control in critically ill, hospitalized patients (42).

Incretin-based approach—As an alternative approach, we recommend that critically ill patients receive incretin-based therapy (liraglutide, 0.6–1.2 mg/day s.c. or exenatide, 5–10 µg bid s.c.) to achieve blood glucose levels in the 90–130 mg/dL range, while avoiding hypoglycemia.

The following approach is both simple and practical. In hyperglycemic patients without prior diabetes history, i.e., stress-induced diabetes, start with or have an incretin onboard pre-, peri-, and postoperatively or in the ICU and continue incretin therapy throughout hospitalization. A number of insulin infusion protocols have been developed for the treatment of hospitalized patients with hyperglycemia (43). If necessary, incretin therapy can be supplemented with insulin using any of these published protocols (43). Incretin therapy has the potential to avoid completely the need for insulin, decrease the amount of basal insulin, avoid insulin boluses, prevent

hypoglycemia, and reduce glycemic variability. In patients previously on insulin, the GLP-1 analog will allow the insulin dose to be reduced or discontinued completely, avoid the need for bolus insulin dosing, and decrease glycemic variability.

In prediabetic and well-controlled type 2 diabetic patients treated with oral antidiabetic agents and who undergo cardiac catheterization or elective surgical procedures, the oral antidiabetic agents (metformin, sulfonyleurea, pioglitazone) should be held on the day of surgery/cardiac catheterization. Ideally, incretin therapy should be started prior to admission and given in the morning of the day of surgery. Postoperatively, most of these patients can be managed with incretin therapy alone. If hyperglycemia is excessive (>150–160 mg/dL), a small amount of insulin, using established protocols, can be added.

Insulin-treated type 2 diabetic patients should be instructed to take their usual dose of basal insulin (glargine, levemir) on the day/night prior to surgery and incretin therapy administered preoperatively and postoperatively as described above.

In poorly controlled diabetic patients on admission or in newly discovered diabetic patients in whom surgery cannot be delayed, intravenous GLP-1 (as per Marso et al. [39]) or subcutaneous GLP-1 receptor agonist therapy should be started and the dose adjusted to achieve the desired level of glycemic control (<120–140 mg/dL). Postoperatively, GLP-1 receptor agonist therapy should be continued and, if necessary, insulin therapy added.

In the medical/surgical ICU, excessive hyperglycemia—whether in previously diagnosed or new-onset diabetic patients or secondary to stress-induced hyperglycemia—can be controlled with an intravenous GLP-1 infusion or GLP-1 analog given subcutaneously without causing hypoglycemia. Stress-induced hyperglycemia responds well to GLP-1 receptor agonist therapy. The need for supplemental insulin can be discerned quickly after starting GLP-1 therapy.

Although gastrointestinal side effects are a potential concern with GLP-1 agonist therapy, the dropout rate in the studies mentioned above has been low (29,30,39). In nondiabetic subjects treated with exenatide, the incidence of nausea can be reduced with ondansetron or metoclopramide (44).

Conclusions—A pathophysiological rationale for intensive glycemic control in critically ill, hospitalized patients exists. However, the benefit of aggressive glycemic control with insulin on morbidity/mortality has been difficult to demonstrate and may be offset by side effects, especially hypoglycemia. We believe that optimizing glycemic control while minimizing hypoglycemia still remains the goal of therapy. In this point-counterpoint debate, we suggest an alternate pharmacologic approach with GLP-1 receptor agonists, for which clinical data continue to accumulate and support their use for the treatment of hyperglycemia in critically ill, hospitalized patients by virtue of their: 1) glucose-dependent release of insulin and glucagon suppression, thereby minimizing hypoglycemia; 2) ability to reverse stress-induced (glucagon and glucocorticoid) hyperglycemia; 3) potential to reduce cardiovascular-related morbidity (Table 1). Although considerable evidence supports the use of GLP-1 receptor analogs in critically ill hospitalized patients with hyperglycemia, well-designed prospective studies comparing these agents with insulin will be required to establish their efficacy and safety.

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