Introduction: intensive insulin therapy in hospitalized critically ill patients

There is no consensus on the in-patient management of patients with Type 2 Diabetes (T2DM) [1,2]. In the United States there are > 6000 surgical/medical intensive care units caring for approximately 31 million patient-days per year [3]. The development of hyperglycemia in patients with and without a history of diabetes is a strong predictor of adverse outcome and mortality [4]. Hospitalized patients with stress-induced hyperglycemia and overt T2DM experience outcomes at a rate that rises in proportion to the severity of hyperglycemia [5–7]. Although some studies have demonstrated a benefit of tight glycemic control with insulin on mortality/morbidity in hospitalized critically ill patients (e.g., patients undergoing coronary artery bypass grafting [CABG] [8], surgical intensive care patients [9], and post–myocardial infarction patients [10]), the results have not been consistent. Results from the Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis study (VISEP) [11], Glucontrol [12], Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-Sugar) [13], and other trials [14] have found no benefit or even increased mortality/morbidity in patients treated with intensive insulin regimens. Hypoglycemia has been a major side effect in all studies that have attempted to achieve tight control with insulin in hospitalized, severely ill patients and may account for the adverse outcomes seen in the above trials [12–15]. Not surprisingly, hypoglycemia (associated with sulfonylurea and insulin therapy) is the most common drug-related side effect in hospitalized patients. A meta-analysis of 29 trials of intensive insulin therapy in intensive care unit (ICU) patients failed to show any reduction in the risk of in-hospital mortality and demonstrated a significantly increased risk of hypoglycemia [16]. Therefore, considerable debate exists concerning in-hospital glycemic goals and the value of intensive insulin therapy. The American College of Endocrinology and the American Diabetes Association consensus conference advocates a plasma target glucose concentration between 140 and 180 mg/dl as a reasonable goal to balance the risks (primarily hypoglycemia) and benefits of intensive insulin therapy in hospitalized patients [17,18]. However, many experts believe that tighter glycemic control would be beneficial if it could be achieved without undue hypoglycemia [19,20].

Incretin therapies

We now examine the benefits of incretin-based therapy (glucagon-like peptide-1 [GLP-1] receptor agonists and dipeptidyl peptidase-4 [DPP-4] inhibitors) in improving glycemic control in hospitalized patients with stress-induced diabetes and in diabetic patients in critical care and non-ICU settings (Table I).

Abstract

Hyperglycemia in patients with and without a prior history of diabetes is an independent marker of morbidity and mortality in critically and noncritically ill patients. Improvement of glycemic control with insulin therapy has been shown to reduce hospital complications in patients with diabetes, but also results in increased rates of hypoglycemia, which have been linked to poor outcomes. Thus, alternative treatment options that can normalize blood glucose levels without undue hypoglycemia are being sought. Incretin-based therapies, such as glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors, stimulate insulin secretion in a glucose-dependent fashion, thus not causing hypoglycemia. Alternative points of view exist regarding insulin versus incretin therapy for the care of these patients. We have brought together the authors on the opposite sides of this discussion with the objective of providing a rational synthesis on how to achieve the best possible control of glycemia in the hospital, using both standard insulin approaches and incretin-based therapies to improve patient outcomes. This review examines the benefits of incretin-based therapy in improving glycemic control in hospitalized patients with stress-induced diabetes and in diabetic patients in critical care and non–critical care settings.

Keywords:
glycemia, incretin, inpatient, type 2 diabetes

History

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<td>Kohl, 2014 [31]</td>
<td>DM and non-DM pts undergoing elective CPB, N = 77; DM, n = 11</td>
<td>1:1 randomization GLP-1 infusion 1.5 pmol/kg/min or PBO</td>
<td>Mean BG overall and during CPB lower by 12.2 mg/dl vs 14.1 mg/dl, GLP-1 vs PBO</td>
<td>None</td>
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<tr>
<td>Sourij, 2009 [32]</td>
<td>Clinically stable with DM, n = 8</td>
<td>GLP-1 IV 1.2 pmol/kg/min or insulin IV, after standard breakfast</td>
<td>GLP-1, lower BG at max and after 2 and 4 h</td>
<td>None</td>
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<td>Deane, 2009 [33]</td>
<td>ICU, non-DM, mechanically ventilated, enteral nutrition, n = 7</td>
<td>GLP-1 IV; 4.5 h 1.2 pmol/kg/min vs placebo</td>
<td>Significantly lower AUC for glucose</td>
<td>None</td>
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<td>Mussig, 2008 [34]</td>
<td>Post-CABG, insulin-naive, T2DM GLP-1, n = 10; Insulin, n = 10</td>
<td>GLP-1 IV; 12 h 3.6 pmol/kg/min vs insulin</td>
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<td>GLP-1: insulin rescue therapy needed for several pts</td>
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<td>Meier, 2004 [35]</td>
<td>2–8 days post–major surgery, fasting, N = 8; DM, n = 8</td>
<td>GLP-1 IV; 8 h 1.2 pmol/kg/min vs PBO</td>
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<td>van Raalte, 2011 [23]</td>
<td>Healthy men receiving prednisone 80 mg, n = 8</td>
<td>Exenatide IV</td>
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<td>Abuannadi, 2013 [36]</td>
<td>Cardiac ICU, n = 40; DM, exenatide, n = 40; historical controls treated with insulin, n = 133</td>
<td>Exenatide infusion up to 48 h 0.025 μg/min</td>
<td>Steady-state BG level was similar between groups</td>
<td>Nausea, n = 16; vomiting, n = 2, no episodes of severe hypoglycemia (&lt; 50 mg/dl)</td>
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<td>Halbirk, 2010 [37]</td>
<td>Ischemic HF, non-DM GLP-1, n = 10; PBO, n = 10</td>
<td>GLP-1 IV; 48 h 1.0 pmol/kg/min vs PBO</td>
<td>GLP-1</td>
<td>GLP-1: hypoglycemic events (n = 8)</td>
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<td>Mecott, 2010 [38]</td>
<td>Severely burned pediatric pts Exenatide, n = 6; IIT, n = 18</td>
<td>Exenatide SC starting at 5 μg q12 up to 10 μg q4 IIT 0.1–1.0 U/kg/h BG target 80–140 mg/dl</td>
<td>Exenatide group required significantly less insulin than IIT group (22 vs 76 IU, respectively)</td>
<td>Incidence of hypoglycemia was similar in both groups (0.38 events/pt-months)</td>
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<td>Sokos, 2007 [39]</td>
<td>Pre- and post-CABG GLP-1, n = 10 (DM, n = 2); insulin, n = 10 (DM, n = 3)</td>
<td>GLP-1 IV; 12 h before to 48 h after CABG 1.5 pmol/kg/min vs standard IV insulin</td>
<td>Significant ]AUC for glucose pre- and intraoperative, no difference postoperative</td>
<td>GLP-1: rescue insulin therapy, n = 5; hypoglycemia, n = 1; control: hypoglycemia, n = 2</td>
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<td>Sokos, 2006 [43]</td>
<td>CHF GLP-1, n = 12 (DM, n = 8); control, n = 9 (DM, n = 5)</td>
<td>GLP-1 SC 5 wks Tx: 1 wk @ 1.25 pmol/kg/min 4 wks @ 2.5 pmol/kg/min</td>
<td>No difference in LVEF</td>
<td>GLP-1: nausea, constipation (n = 5); increase in HR; hypoglycemia, n = 4 (9 episodes); control: hypoglycemia, n = 2 (4 episodes)</td>
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<td>Nikolaidis, 2004 [40]</td>
<td>Acute MI, LVEF &lt; 40% GLP-1, n = 10 (DM, n = 5); control, n = 11 (DM, n = 4)</td>
<td>GLP-1 IV; 72 h post angiography 1.5 pmol/kg/min vs standard therapy</td>
<td>Glycemic control similar between groups; GLP-1 significantly ]LVEF, global and regional wall motion indices</td>
<td>GLP-1: nausea (n = 4), vomiting (n = 2), constipation (n = 2), reduced appetite (n = 2), asymptomatic hypoglycemia (n = 2)</td>
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Glucagon-like peptide-1 is secreted by the L-cells of the gastrointestinal tract and, in conjunction with glucose-dependent insulinotropic polypeptide, accounts for >90% of the incretin effect, that is, the 2- to 3-fold greater release of insulin from β cells following oral versus intravenous glucose administration [21]. The stimulatory effect of GLP-1 on insulin secretion, as well as its inhibitory effect on glucagon secretion, is glucose dependent [21]. Thus, as the plasma glucose concentration declines to normoglycemic levels, the stimulatory effect of GLP-1 on insulin secretion wanes, as does its inhibitory effect on glucagon secretion. This provides a normal physiologic mechanism to prevent hypoglycemia. Of note, excess steroids, whether of endogenous (i.e., stress-induced) or exogenous origin, cause hyperglycemia, both by promoting insulin resistance and inhibiting insulin secretion. The GLP-1 receptor agonists have a potent effect to overcome the pathway in the β cell that is inhibited by glucocorticoids and augment insulin secretion [22-24].

Moreover, considerable data indicate that GLP-1 exerts multiple beneficial effects on the heart [25], and preliminary analysis suggests that GLP-1 receptor agonists may reduce cardiovascular outcomes in diabetic patients [26].

Because the half-life of GLP-1 is short, ~2 minutes, incretin-based therapies rely on (1) the inhibition of DPP-4, the enzyme that inactivates endogenously secreted GLP-1; or (2) administration of exogenous GLP-1 receptor agonists that are resistant to DPP-4 degradation. Four DPP-4 inhibitors (sitagliptin, saxagliptin, linagliptin, and alogliptin) and 2 shorter-acting GLP-1 receptor agonists (exenatide and liraglutide) currently are available. The increase in plasma GLP-1 levels with the DPP-4 inhibitors (1.5- to 2-fold above baseline) is modest compared to the 4- to 5-fold increase observed with the GLP-1 analogues [27]. Not surprisingly, the GLP-1 receptor agonists are more potent in reducing plasma glucose levels and hemoglobin A1c (HbA1c) in T2DM patients than the DPP-4 inhibitors [27]. Nonetheless, the DPP-4 inhibitors have been shown to be effective in reducing hyperglycemia in hospitalized noncritically ill patients [28,29], likely by their effect to inhibit the secretion of glucagons [30] and oppose the cortisol-induced inhibition of insulin secretion [23,24].

### Beneficial metabolic and cardiovascular effects of incretins

Native GLP-1, as well as GLP-1 receptor agonists such as exenatide and liraglutide, have been shown to exert a number of metabolic effects that are advantageous in hospitalized patients (Table I) [23,25,29,31–43]. In both nondiabetic and diabetic patients undergoing CABG, GLP-1 infusion prior to anesthesia resulted in improved glycemic control [31], and GLP-1 infusion for 12 hours after CABG in 20 insulin-naive T2DM patients resulted in glycemic control similar to that in the insulin-treated control group [34]. Perioperative treatment with GLP-1 in 20 patients undergoing CABG resulted in better glycemic control, lower postoperative insulin levels, and fewer arrhythmias compared with controls [39]. A GLP-1 infusion in patients with T2DM after major surgery resulted in normalization of blood glucose levels,
suppression of glucagon secretion, and an increase in insulin secretion [35], whereas GLP-1 infusion in critically ill, nondiabetic patients receiving intraduodenal nutrient infusion markedly attenuated the glycemic response to enteral nutrition [33].

Use of the GLP-1 receptor agonist exenatide has been shown to be beneficial in other hospital settings. The administration of subcutaneous exenatide was shown to normalize blood glucose levels in patients receiving prednisone [22] and to improve/normalize blood glucose levels in nondiabetic patients undergoing various surgeries when given perioperatively [30]. Exenatide also has been shown to improve glycemia in diabetic patients in a cardiac ICU [36], in severely burned pediatric patients [38], and in posttransplant patients [44]. An integrated analysis of clinical trials in patients with T2DM showed that the relative risk of cardiovascular events, including stroke, myocardial infarction, cardiac mortality, acute coronary syndrome, and revascularization procedures, with exenatide was 0.7, suggesting that exenatide use did not increase, and may even decrease cardiovascular risk [26].

A number of mechanisms responsible for cardioprotective effects of GLP-1 receptor agonists have been suggested [25], including enhanced myocyte viability after ischemic injury [45], increased systolic function in humans [39,40,43], coronary artery vasodilation [46], and increased sodium excretion [47]. Although DPP-4 inhibitors have been suggested to have potential cardiovascular benefit, 2 recent large prospective studies in high-risk T2DM patients failed to show a reduction in myocardial infarction, stroke, and death with saxagliptin and alogliptin [48,49].

**Incretin therapy in hospital patients: process of care**

In hospitalized patients with stress-induced and steroid-induced diabetes, as well as in patients with overt diabetes, we have found, in the context of clinical reasoning applied to evidence-based medicine [50] that DPP-4 inhibitors and GLP-1 receptor agonists (1) effectively reduce the mean blood glucose level while minimizing the risk of hypoglycemia; (2) decrease excessive glycemic excursions that result from the release of stress hormones (glucagon and glucocorticoids); (3) reduce or eliminate the need for insulin (both the basal insulin requirement and the need for prandial insulin boluses); (4) reduce glycemic variability, which has been postulated to promote adverse outcomes in hospitalized patients; and (5) have no undue cardiovascular side effects.

These observations are supported by published studies. In a pilot study, Umpierrez et al. [29] studied the effect of sitagliptin in hospitalized (on general medical/surgical wards) patients with T2DM who were treated with diet, oral agents, or low doses of insulin (≤ 0.4 units/kg/day) and who had moderately elevated blood glucose levels (< 180 mg/dL and HbA1c < 7.5%). There were no differences in glycemic control between diabetic patients randomized to sitagliptin alone, sitagliptin plus basal glargine insulin, or basal (glargine)-bolus (lispro) insulin. Patients receiving sitagliptin needed significantly lower total daily insulin doses and fewer insulin injections compared with those treated with the basal-bolus insulin regimen. Patients with moderate hyperglycemia (blood glucose < 180 mg/dL) who received sitagliptin plus correction doses of rapid-acting insulin responded as well as those treated with the basal-bolus insulin regimen. The results of this pilot study suggest that treatment with sitagliptin alone or in combination with basal insulin represent an effective alternative to the basal-bolus insulin regimen that usually is employed to treat T2DM patients who are admitted to general medicine and surgical wards. However, the use of DPP-4 inhibitors to treat critically ill, hospitalized patients in surgical/medical ICUs has not been studied. Because DPP-4 inhibitors are less potent than the GLP-1 receptor agonists in promoting insulin and inhibiting glucagon secretion [27,51], it is likely that they will be less efficacious in controlling hyperglycemia in these more critically ill patients.

In a recently published study, Abuinendi et al. [36] administered intravenous exenatide (bolus = 0.05 μg/min for 30 minutes; continuous infusion = 0.025 μg/min) to 40 adults admitted to the cardiac ICU. Within 3.9 hours, exenatide reduced and maintained the plasma glucose from 199 mg/dL to 140 mg/dL for the subsequent 48 hours. Blood glucose levels < 70 mg/dL were uncommon. Deane et al. [33,52] have shown that GLP-1 infusion (1.2 pmol/kg/min) effectively reduced the glycemic response to small intestinal nutrient administration in critically ill, hospitalized patients in a randomized double-blind study in patients with [33] and without [52] T2DM. Using a similar infusion protocol, Kohl et al. [31] demonstrated that GLP-1 (1.5 pmol/kg/min) effectively reduced blood glucose levels compared to placebo in 77 patients (both diabetic and nondiabetic) undergoing elective cardiac surgery with cardiopulmonary bypass. Similar beneficial results on glycemic control have been reported in patients undergoing CABG surgery [34,39], and Meier et al. [35] observed that GLP-1 infusion (1.2 pmol/kg/ min) between the second and eighth hospital day achieved normoglycemic blood glucose levels within 150 minutes after major surgery in T2DM patients with good tolerance and without hypoglycemia. The pros and cons of GLP-1 versus insulin therapy for critically ill, hospitalized patients have been the subject of recent reviews [1,2].

When using incretin therapy, the proposed approach is both simple and practical. We recommend that patients with prediabetes (HbA1c = 5.7%–6.4%, fasting plasma glucose = 100–125 mg/dL, 2-hour post–oral glucose tolerance test or random postprandial glucose = 140–199 mg/dL), with undiagnosed diabetes, or with known diabetes be identified before elective admission, as it is predictable that their sugars will rise in the hospital to a degree requiring therapy according to the existing guidelines. The basic principle in these patients, as well as in those without a previous history of diabetes but who present with new-onset hyperglycemia in the hospital (i.e., stress-induced diabetes), is to start with or have an incretin on-board pre-, peri- and postoperatively, or in the ICU, and to continue the incretin therapy throughout the hospitalization and after discharge.

Usual renal-adjusted doses of any DPP-4 inhibitor should be employed and can be given orally or via nasogastric tube.
Incretins are safest if administered prior to the use of insulin because adding incretins to insulin may carry a risk of hypoglycemia if the insulin dose is not reduced. All DPP-4 inhibitors are approved in combination with insulin and have an excellent safety record. Exenatide and liraglutide can be used at their recommended starting doses and titrated as tolerated. In our clinical experience, as well as in published in-hospital studies [34,37,39], the incidence of nausea/vomiting is low. Hospitalized patients eat less food and eat more slowly; their diet is not high in fat and fiber content, and they can be admonished to stop eating when they have the first sense of fullness. Those patients who do report gastrointestinal upset or nausea can be managed with metoclopramide or ondansetron [53]. Incretin use should be avoided in patients with a history of pancreatitis.

In patients with recently diagnosed or established diabetes, in patients with stress-induced diabetes, and in patients with perioperative or illness-related hyperglycemia (i.e., due to elevations in 2 stress hormones, glucagon and cortisol, that are responsive to incretin medications) [23,24], the glucose-lowering efficacy of the DPP-4 inhibitors is effective to avoid the need for 20 to 30 units of insulin, whereas the GLP-1 receptor agonists are effective to 40 to 60 units [1]. Noncritically ill patients admitted to general surgical/medical wards, that is, similar to those patients reported by Um呲ierre et al. [29], are candidates for initial DPP-4 inhibitor therapy, whereas those who are on higher doses of insulin as outpatients or who are more critically ill are better suited for initial therapy with a GLP-1 receptor agonist.

When starting incretins in patients on insulin, understanding the potential effectiveness of the incretin is important because the physician has to decide by how much to reduce the insulin dose when initiating incretin therapy. All GLP-1 analogues discussed work quickly with the first dose. Exenatide normally is given by subcutaneous injection but also can be given as a continuous intravenous infusion (bolus = 0.05 μg/min for 30 minutes; continuous infusion = 0.025 μg/min) as recommended by Abuannadi et al. [36]. The dose can be up-titrated based on tolerance and the desired level of glycemic control. Recent studies with the use of incretin therapy for the management of hyperglycemia in hospitalized patients indicate starting a GLP-1 receptor agonist, exenatide (5 μg bid) or liraglutide (0.6 mg/day), by subcutaneous injection, with titration as necessary. During the initial 24 hours, a supplemental order for rapid-acting insulin can be included, and after 24 hours the insulin regimen can be changed to a single basal injection if necessary. Short-acting exenatide and once-daily liraglutide have been approved for use in combination with basal insulin. Incretin therapy can be supplemented with insulin using any insulin protocol/ regimen that routinely is employed at one’s institution. It is important to note that this process of care concerning incretin use in the hospital does not require any change of existing insulin protocols/order sets in order to implement.

In prediabetic and well-controlled T2DM treated with oral hypoglycemic agents and who undergo cardiac catheterization or elective surgical procedures, the oral hypoglycemic agent (metformin, sulfonylurea, pioglitazone) should be withheld on the day of surgery/cardiac catheterization. Ideally, incretin therapy (GLP-1 receptor agonist or DPP-4 inhibitor) should be started (or continued if the patient already is receiving incretin therapy) prior to admission and given in the morning of the day of surgery. Intraoperative use of glucose solutions, which can generate glycemic spikes, should be avoided. Postoperatively, many of these patients can be managed successfully with incretin therapy alone. If hyperglycemia is excessive (> 150–160 mg/dl), incretin therapy can be supplemented by rapid-acting insulin.

Poorly controlled insulin-treated diabetic patients can be treated with a combination of basal insulin and incretin prior to or shortly after the hospitalization. The total daily dose of insulin should be adjusted appropriately to avoid hypoglycemia. Patients should be instructed to take their usual dose of basal insulin (glargine, detemir) on the night/day prior to surgery. Incretin therapy has the potential to enable discontinuation of insulin, especially as the patient can be encouraged to follow a diet more rigorously in the monitored hospital setting.

In diabetic patients with poor glycemic control on admission, who are discovered to have new-onset diabetes in whom the operative procedure cannot be delayed, subcutaneous (or intravenous) GLP-1 receptor agonist therapy should be started and the dose adjusted to achieve the desired level of glycemic control. Postoperatively, on the ward or in the ICU setting, the GLP-1 agonist therapy should be continued. Insulin therapy can be added if necessary.

Conclusion

We described a process of care that employs incretin therapy to achieve normo-/near normoglycemic control (premeal blood glucose of 80–140 mg/dl) in hospitalized patients, while minimizing the risk of hypoglycemia and capturing those cardiovascular benefits that accrue by achieving tight glycemic control. The approach is simple and practical, is not associated with significant side effects, and does not require alteration of existing in-hospital protocols. We look forward to and encourage more clinical research to further validate and gain more experience with the incretin-based therapeutic approach. Based on (1) evidence-based practice, (2) knowledge about the pathophysiology of stress-induced diabetes in critically ill hospitalized patients, (3) the known mechanism of action of incretin hormones, (4) the excellent benefit/risk ratio of incretin therapy, and (5) the encouraging published results with incretin-based therapy, we believe that this approach has significant advantages (especially the lack of hypoglycemia) over insulin therapy and, if necessary, can be combined with insulin.

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