Management of Hyperglycemia in the Hospitalized Podiatric Medical Patient

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With the growing prevalence worldwide of diabetes mellitus and hyperglycemia, hospital-based health-care professionals will encounter patients with these conditions with increasing frequency. It is well known that long-term control of blood glucose reduces the rate and severity of complications in patients with diabetes, but there is also mounting evidence that even short-term glycemic control in hospitalized diabetic patients can significantly lower morbidity and mortality in many areas, from nosocomial infection to postoperative course. The results of traditional approaches to controlling blood glucose in hospitalized patients have been disappointing owing to a variety of factors, including the use of oral agents that are difficult or dangerous to use in inpatients, older insulin preparations with unphysiologic modes of action, and even provider reluctance to accept glycemic control as an essential element of the care of the diabetic hospitalized patient. This article provides guidelines for the effective management of hyperglycemia in these patients throughout the hospital stay, with specific recommendations for the perioperative, operative, and postoperative periods. (J Am Podiatr Med Assoc 94(2): 135-148, 2004)

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The incidence and prevalence of diabetes mellitus and its precursor states (hyperinsulinemia—insulin resistance, the metabolic syndrome, and impaired glucose tolerance) are increasing exponentially in both the United States and the rest of the world. Healthcare professionals will find themselves more frequently having to attend to the difficulties and implications of managing hyperglycemia and hyperglycemic states in patients admitted to the hospital for reasons related and unrelated to the hyperglycemia. Much information has been gained experimentally and observationally regarding the impact of other illness on diabetes mellitus and its management, as well as vice versa.

Hyperglycemia affects patients from the moment they arrive at the hospital; several studies suggest that a single hospital admission glucose level serves as a marker for future inpatient morbidity and mortality. Untreated or poorly treated hyperglycemia during hospitalization is known to be a significant risk factor in the response to infection, increases the risk of nosocomial and postoperative infections, and lowers survival rates in coronary artery disease as well as critical illness requiring surgery and intensive-care-unit treatment. These risks from in-hospital hyperglycemia are additional to the long-term chronic complications previously shown to be responsive to long-term glucose management.

Traditional standards of therapy for the inpatient management of diabetes mellitus have come under increasing scrutiny during the past decade, leading to some surprising and disappointing results. At the same time, these investigations have led to new insights into the care of diabetic patients.

Any given hospitalization may serve as the first proof of, and portal to, the diagnosis and treatment of diabetes mellitus—especially type 2 diabetes. Most patients with type 2 diabetes already have a chronic complication related to long-standing hyperglycemia when the diagnosis is made, and the average time to diagnosis of type 2 diabetes in the US pop-
ulation is approximately 5 to 10 years. Thus not only may the hospital serve as the arena for treatment of the patient’s primary condition, but also hospitalization may enable physicians to diagnose and treat diabetes earlier, thereby preventing chronic complications.

Epidemiology

Prevalence of Diabetes Mellitus in the General Population

There are approximately 16 million known diabetic individuals in America. An estimated one-third more do not know that they have the disease. More than 90% of all patients with diabetes mellitus have the type 2 form. Most patients developed the disease through a combination of genetics, sedentary lifestyle, and injudicious diet. Indeed, we are truly experiencing a pandemic of diabetes in the United States and throughout the world. Rapidly increasing rates of obesity in children as well as adults have been documented in the recent past. Because obesity is at the heart of the development of type 2 diabetes mellitus, at the current rate of increase, it is expected that in the United States there will be 24 million known patients with diabetes by 2010.

Prevalence of Diabetes Mellitus in the Inpatient Population

The emerging pandemic of diabetes has serious implications for the future. Even now, while the average prevalence of diabetes in the general population is approximately 6%, at any given time, a review of the inpatient census at any general hospital would show that 30% to 50% of inpatients have diabetes. This is at least in part because of the diabetic patient’s significantly higher probability of being hospitalized for treatment of an infection, atherosclerotic cardiovascular disease, or a metabolic disorder. Imagine the result if current trends continue and the prevalence in the general population merely doubles to 10% to 15% during the next 10 years.

Clinical Impact

Effect of Chronic Hyperglycemia

The effects of chronic hyperglycemia and its two frequent attendants—hypertension and hyperlipidemia—are well known. Increased rates of atherosclerotic cardiovascular disease make the incidence of acute coronary syndromes, cerebrovascular accidents, and peripheral vascular disease four to six times more likely. However, it is now well documented that there is a 30% to 60% decrease in chronic complications with long-term glycemic control in types 1 and 2 diabetes mellitus.

Effect of Acute Hyperglycemia

Acutely, hyperglycemia is known to interfere with protection against infection in almost every step, from opsonization to white blood cell movement, phagocytosis, intracellular killing power, and wound healing. More important, correction of acute hyperglycemia has demonstrated improvement in these defense mechanisms, with better surgical and postsurgical outcomes.

Other benefits of aggressive control of glucose levels in diabetes have also been discovered. In the DIGAMI study, the outcomes of patients experiencing an acute myocardial infarction who received an insulin infusion were markedly better almost immediately than those of the control group of patients with acute myocardial infarctions who did not receive the insulin infusion. In addition, in a study of surgical intensive-care-unit patients, those with insulin infusions and aggressive control of glucose to normal levels experienced improvements in morbidity and mortality in diverse areas, such as number of episodes of sepsis, time greater than 2 weeks receiving ventilatory support, and both intensive-care-unit and overall in-hospital mortality—the latter two being decreased by almost 50%.

Current Considerations

A new paradigm is emerging of much tighter blood glucose control in patients with diabetes who are hospitalized—indeed, in all hospitalized patients with hyperglycemia, not just those previously diagnosed as having diabetes mellitus. This places even more emphasis on the physician’s obligation to understand and properly use the various tools at his or her disposal to safely achieve the degree of glucose control that has been shown to reduce in-hospital morbidity and mortality. Figure 1 demonstrates the contrast between the old and new glucose-control paradigms.

Measurement of Blood Glucose Concentration

Any discussion of achieving better glucose control in an inpatient setting must begin with a basic premise: the availability of timely measurement of the pa-
tient’s glucose level. Unfortunately, this measurement is not routinely available in many hospitals. The burgeoning number of hospitalized patients with hyperglycemia, the need to perform multiple assays rapidly and almost simultaneously, the need for multiple assessments in each patient every day, and the need for virtually instantaneous performance of glucose testing in cases of suspected hypoglycemia all make the traditional venipuncture-drawn, automated, laboratory-machine glucose determination obsolete, frequently unhelpful, and unnecessarily uncomfortable. The mandatory time delay between performance of the test and use of the measurement renders the determination problematic; the amount of blood necessary with venipuncture versus a capillary determination is eminently wasteful, and the repeated injury to venous architecture by phlebotomy is painful and morbid.

The availability of relatively inexpensive handheld glucose meters with rapid-to-instantaneous readouts of capillary measurements has expanded greatly during the past 5 to 10 years. Meters are made in individual and hospital versions, with the latter including such modern conveniences as built-in quality checks, database preservation of operator and patient characteristics, and even instantaneous wireless transmission to a nearby network for immediate incorporation into a laboratory database. These glucose meters require as little as 1 to 5 µL of blood (compared with 3 to 5 mL of venipuncture-acquired blood), are easy to use, and can be readily applied at the bedside. Reliance on the availability of point-of-service, handheld, capillary-determination glucose meters throughout the hospital is rapidly becoming the new standard in diabetes management.

**Choice of Glucose-Controlling Agents: Oral Agents**

The past decade has witnessed an explosion in the number and types of oral agents available for the treatment of type 2 diabetes mellitus. Each has its particular benefits and drawbacks. In the outpatient setting, the knowledgeable physician often “mixes and matches” these new agents in accordance with the patient’s individual needs and comorbidities. In the inpatient setting, however, the usefulness and even safety of these agents are much more limited.

Because of the diverse and sometimes unpredictable reasons that glucose levels may change in the hospitalized patient, and the rapidity with which these changes can occur, long-acting oral medications represent a potentially dangerous source of complications and increased morbidity. The use of metformin provides one example of such a scenario. When a patient is in the fasting state, is preoperative or perioperative, or is acutely or gravely ill, the use of metformin can be very dangerous and even lethal through the production of lactic acidosis. By understanding the drawbacks, limitations, and interactions of oral agents used for the control of glucose in the hospitalized and perioperative patient, the clinician can be on guard to prevent or ameliorate them.

**Sulfonylureas**

Sulfonylureas act by stimulating insulin release from the pancreas. Older, or “first-generation,” sulfonylureas, such as tolazamide, tolbutamide, and chlorpropamide, are now infrequently used because they can cause a syndrome of inappropriate antidiuretic hormone secretion–like effect and a disulfiram-like reaction (severe abdominal pain with alcohol ingestion). In addition, chlorpropamide, with its 24-hour half-life, has been associated with severe and prolonged hypoglycemia that is frequently fatal, especially in the elderly and the malnourished.

Second-generation sulfonylureas, e.g., glipizide and glyburide, have a proven track record of use in the community and are used frequently as first-line agents. Cardiovascular toxicity, a concern with first-generation sulfonylureas, has not generally been associated with glyburide or glipizide. However, extended periods of hypoglycemia may still occur in the elderly patient with glyburide treatment. Glimepiride, an agent closely related to glipizide and glyburide, is some-
times considered a “third-generation” sulfonylurea because of its insulin-stimulatory effects; however, for purposes of discussion of treatment of inpatients with diabetes, its behavior is almost identical to that of glipizide and glyburide. These agents only rarely cause a syndrome of inappropriate antidiuretic hormone secretion–like effect or a disulfiram-like reaction. However, even these agents depend on intact B-cell function to work, can cause hypoglycemia in the absence of food, and, depending on the formulation chosen, still have half-lives of 4 to 6 hours. Only the most stable of hospitalized patients with diabetes mellitus should continue taking these agents in the hospital environment; for the same reasons, great caution should be exercised in initiation of these agents in the hospitalized patient.

**Meglitinides**

The meglitinides are a new and heterogeneous class of sulfonylurea-like agents that stimulate insulin release from the B cell but do so prejudiciously in the presence of food and only for a relatively short period. These two characteristics make the meglitinides attractive for the long-term treatment of type 2 diabetes because they provide for insulin “on demand” and leave the preprandial, or fasting, state without substantial levels of circulating insulin. Chemically, repaglinide (Prandin; Novo Nordisk Pharmaceuticals, Inc, Princeton, New Jersey) and nateglinide (Starlix; Novartis Pharmaceuticals, Inc, East Hanover, New Jersey) are quite different from each other, with the former being a benzoic acid derivative and the latter being a d-phenylalanine derivative. However, in clinical practice, their use, safety, and effectiveness are remarkably similar. Their main limitations are a rather low degree of efficacy in controlling glucose levels as monotherapy compared with other available agents and their high cost. In the hospitalized patient, the use of these agents would be expected to be accompanied by a larger margin of safety compared with longer-acting sulfonylureas because these medications are administered only when the patient eats. Therefore, should a patient’s oral eating status change suddenly, the medication is simply withheld. Because of the shorter half-life of these agents, previously administered doses are metabolized more quickly, and therefore the risk of a hypoglycemic episode is reduced.

**Thiazolidinediones**

Pioglitazone (Actos; Eli Lilly and Co, Indianapolis, Indiana) and rosiglitazone (Avandia; GlaxoSmithKline, Research Triangle Park, North Carolina) constitute the available members of a class of agents called thiazolidinediones. These agents are said to work by stimulation of a family of nuclear receptors called peroxisome proliferator activation receptors, which causes an increase in insulin sensitivity, mainly by means of an increase in the recruitment and production of intracellular glucose transporters. These agents have many diverse and parallel actions apart from glucose control, and many studies are under way to determine whether actions besides pure glucose control have an impact on long-term morbidity or mortality in patients with type 2 diabetes mellitus. For the hospitalized patient, however, considerations for the use of thiazolidinediones are more limited. Thiazolidinediones require 4 to 6 weeks to reach their peak effectiveness. Therefore, they would be considered an inappropriate choice for a dependable and newly instituted form of therapy for the control of glycemia in type 2 diabetes mellitus in the hospitalized patient. In addition, in states of impaired cardiac function, new or worsening fluid retention and congestive heart failure have been noted. Finally, although in clinical practice these second-generation thiazolidinediones have been exceedingly safe with regard to hepatic dysfunction, unlike their predecessor troglitazone, caution should be exercised in instituting or continuing use of these agents in patients with known or suspected hepatic dysfunction.

Use of these agents should be continued in patients who previously had been using them safely and with efficacy, those who are medically stable, and those who do not have a compromised cardiac or hepatic status. Initiation of these agents in the hospitalized patient is not generally recommended.

**Metformin**

Metformin belongs to the biguanide class of agents. Its exact mechanism of action is unknown, but it seems to work in the liver; it reduces hepatic glucoseogenesis, increases hepatic glucose uptake, and slightly improves insulin resistance in the periphery. Its predecessor, phenformin, was associated with fatal lactic acidosis in an unacceptable number of patients and so was withdrawn from the market in 1977. Metformin was approved by the US Food and Drug Administration in 1994, and it is associated with a significantly decreased incidence of lactic acidosis compared with phenformin (approximately 1 in 33,000 cases). However, when lactic acidosis is present, it is fatal in more than 50% of patients. One of the most discussed potential metformin-associated toxicities was that seen in the United Kingdom Prospec-
tive Diabetes Study wherein metformin added to sulfonylurea therapy increased cardiovascular death by almost 100%. Consequently, patients are now instructed to stop taking metformin 48 hours in advance of any radiographic procedure in which contrast is used and before any surgical procedure in which general anesthesia, dehydration, or the nothing-by-mouth state could be encountered; therapy should not start again for 24 hours after the procedure and only after ensuring effective renal flow and production of urine. Although many authorities have recommended discontinuation of metformin therapy in the hospitalized patient, studies have demonstrated not only patently inappropriate continuation in hospitalized patients but, even more distressingly, its initiation in wholly inappropriate patient populations, such as those with acute myocardial infarction, renal insufficiency, and even frank renal failure.

Choice of Glucose-Controlling Agents: Insulin

Treatment with insulin is indicated when it is deemed inadvisable to continue or initiate oral agent therapy in the hospitalized patient with type 2 diabetes. For the patient with a previously stable regimen of oral antidiabetic agents, resumption of the same regimen and discontinuation of insulin can occur on hospital discharge. For patients suspected or known to have had type 2 diabetes but who had not previously established an oral treatment regimen, provision for continuation of the insulin regimen, with “dovetailing” of an oral regimen simultaneous with the tapering of the insulin on discharge, is often recommended.

Insulin Therapy

Achieving near euglycemia and the accompanying improvements in nosocomial infections, postoperative outcome, treatment of acute cardiovascular disease, and survival during intensive-care-unit treatment of the diabetic patient is highly desirable yet often problematic in practice. Multiple variables contribute to the potential for wide glycemic excursions and suboptimal glucose control, including changing the nothing-by-mouth versus fed status of patients for radiologic studies, surgical interventions, and unexpected nausea or emesis; the inherent variability in the delivery times of meals on any given hospital floor; staff overload, resulting in late or omitted insulin doses; and the consideration that each individual insulin preparation has its own particular profile of action. In addition, many insulin preparations are potentially difficult to use safely in hospitalized patients because of rapid changes in the status that can occur in these patients.

Figure 2 demonstrates the normal rise in glucose concentration that accompanies the prototypical three meals a day (and bedtime snack). In the individual without diabetes mellitus, the normal pattern of insulin secretion exactly mimics this pattern; as a result, normoglycemia is maintained. In attempting to imitate this pattern with injected insulin, various schedule permutations and preparations have been used. A basic approach is illustrated here.

Regular insulin is said to have an onset of 30 to 45 min, a peak at approximately 2 hours, and a biologic effectiveness of more than 4 hours. Therefore, until the past 10 years it was the most popular insulin for covering the meal-associated increases in glucose levels that occur in diabetes. On the other hand, NPH-modified insulin is said to have an onset of 1 to 2 hours, a smooth rise to an extended peak at approximately 8 hours, and a diminution of action to virtually zero by 12 to 14 hours. It is therefore best used to cover the “basal” or continuing background requirement for insulin over time in a patient with diabetes. These are what we would call the insulin preparation’s “best curves” (Fig. 3).

Under “real-world” conditions, however, the performance of even the previously most popular insulin preparations deviates from their best curves, with NPH deviating more than regular insulin (Fig. 4). Imagining, for the moment, that these insulins would continue to behave under their best curve profiles (Fig. 5), and even with multiple different programs of administration, much time is still spent above the required level of insulin late after meals, potentially causing hypoglycemia. Concomitantly, however, the rate of onset of action of regular insulin is almost always too low for physiologic absorption of glucose at the time of the meal; thus significant immediate postprandial hyperglycemia is not prevented. Fortunately, newer insulin preparations are available that allow for a superior level of control.

Figure 2. Normal glucose level rises during and between meals in the nondiabetic individual.
Newer Preparations of Insulin

By virtue of modification of one or two amino acids on the native human insulin A and B chains, profound and useful changes in insulin action profiles can be demonstrated that significantly increase our ability to imitate normal insulin secretion.

Insulin Lispro

In 1996, insulin lispro (Humalog; Eli Lilly and Co) was approved by the US Food and Drug Administration. At the time, it was the first and only recombinant DNA, manufactured human insulin and the first short-acting insulin analog. By switching amino acids 28 (proline) and 29 (lysine) on the B chain of human insulin (Fig. 6), the activity of the insulin is dramatically altered. Its absorption is ultra-rapid (occurring within 5 to 15 min, compared with 30 to 45 min with regular insulin), its peak is early and sharp at 30 to 45 min (compared with 2 to 3 hours with regular insulin), and it lasts only 60 to 90 min (compared with 4 to 6 hours with regular insulin). This profile imitates almost exactly the natural sharp peak of insulin secretion that occurs when a meal is eaten. In fact, because the onset of action of lispro is so rapid, patients are warned not to take the injection until “the food is on the fork” so as to prevent sudden, severe hypoglycemia. Furthermore, because the “tail end” of lispro action is so much shorter than that of regular insulin, postprandial intermeal hypoglycemia is much less frequent with the use of lispro. Therefore, one can achieve better control of the prandial peak along with less postprandial hypoglycemia.

This action has obvious implications for use in the hospital. In patients in whom oral intake is not a certainty because of postoperative nausea and other factors, physicians can allow patients to eat what they can and administer the lispro during or immedi-

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**Figure 3.** “Best curves” action profiles, under ideal conditions, of regular and NPH insulin.

**Figure 4.** “Actual” action profiles of regular and NPH insulin in clinical practice.

**Figure 5.** Superimposition of regular insulin and NPH insulin “best curves” on actual glycemic excursions. A, Three-injection regimen of NPH (long-lasting/basal) insulin and regular (short-acting) mealtime insulin. B, Three-injection regimen of NPH insulin and regular insulin using the “split-mixed” method of combination. C, Four-injection regimen with NPH insulin and regular insulin attempting to imitate physiologic insulin release.
ately after the meal. Because of the rapid action of insulin lispro, postprandial glucose control is still much better than with regular insulin. One drawback of lispro resides in the very same characteristic of rapid action: nursing staff cannot give patients their morning injection of lispro without the food tray actually being present. There is little margin of error here, and “preadministration” of a mealtime bolus of lispro on nursing medication rounds, without the benefit of available food, risks the onset of a hypoglycemic episode.

**Insulin Glargine**

Introduced in 2001, insulin glargine (Lantus; Aventis Pharmaceuticals, Kansas City, Missouri) has done for long-acting basal insulins what lispro did for short-acting insulins. With glycine substituted for aspartagine at position 21 on the A chain and two arginines added to the C-terminus of the B chain of human insulin (Fig. 7), the action profile (Fig. 8) is changed to that of a long-acting basal insulin that has almost no peak whatsoever and that lasts on the order of 20 to 24 hours, with much better interpatient as well as intrapatient stability and reproducibility. This flatter, longer, more reproducible curve essentially substitutes for the basal portion of our insulin requirements and, when paired with insulin lispro, almost exactly duplicates normal insulin secretory physiology (Figs. 9 and 10).

Two clinical characteristics of insulin glargine merit mention here: its immiscibility with other insulins and its colorless solution. Because of the biomechanics of insulin glargine’s low pH as part of its extended action, it cannot be mixed with other insulins in the same syringe. To do so would cause unpredictable aberrancies in the time course of both insulins. Therefore, insulin glargine is usually administered at bedtime so that psychologically the patient does not feel that he or she is injecting “extra” doses, since short-acting insulins are generally not used at night. However, a recent article about morning versus bedtime use of insulin glargine versus NPH demonstrated that the best overall control and the least amount of hypoglycemia occurred in the cohort injected with insulin glargine in the morning. A more troublesome clinical characteristic is the colorless nature of insulin glargine. All previous short-acting insulins had been colorless in nature, whereas all previous intermediate- or long-acting insulins, having been suspensions, were “milky” or cloudy in nature and therefore could be easily distinguished by sighted people (in this instance by nursing staff), providing an extra layer of drug-administration safety. In the case of insulin glargine, however, its colorless nature could lead, and indeed has led, to confusion on the part of nursing staff and patients alike. Whereas substitution of a small amount of insulin glargine for insulin lispro (eg, 4 to 10 U) at the time of a meal would do little but allow significant postprandial hyperglycemia for that meal, substitution of 20 to 30 U of insulin lispro for insulin glargine at bedtime could precipitate a severe, life-threatening hypoglycemic reaction.

**Insulin Aspart**

Insulin aspart (NovoLog; Novo Nordisk Pharmaceuticals, Inc), more recently introduced into clinical use, adds to the number of ultra-short-acting insulin analogs. Its chemical structure includes a substitution of aspartic acid for proline at position 28 on the B chain of human insulin (Fig. 11). Its clinical characteristics are similar to those of insulin lispro.
Insulin Administration

Sliding Scale versus Basal-Bolus or Insulin Infusion

Use of the traditional sliding scale of insulin replacement does not usually achieve the necessary degree of glucose control. The use of sliding scales generally seems to have been a protection against the administration of unduly large amounts of insulin to patients who, when not eating, would then have hypoglycemic reactions. This mindset seems to have its genesis in the days when there was a more limited selection of different insulin formulations, each with unpredictable and, for a hospitalized patient, unacceptable action profiles, as well as the lack of an ability to instantly, accurately, and repeatedly monitor capillary blood glucose levels so as to preempt severe hypoglycemia. As a trade-off in this situation, patients would be allowed to “run a little high/sweet.” When (and if) blood glucose concentration was measured and was found to be extraordinarily high, supplemental insulin would be administered.

The major pitfall of this approach is that in the absence of an adjunct basal insulin underlying the episodic need for superimposed bolus insulin, immediate hypoglycemia is commonly followed by rebound hyperglycemia, the loss of action of the short-acting insulin, causing hyperglycemia, or both, requiring another large bolus of short-acting insulin. In this way, a cycle of widely fluctuating glucose levels, or “roller-coastering,” occurs (Fig. 12).

Because of the drawbacks associated with older formulations of insulin, as well as those associated with sliding-scale-only coverage of hyperglycemia, a new approach is needed. For the nonperioperative, non–critically ill hospitalized patient with diabetes mellitus, the simplest effective approach is to use...
combination of a long-acting basal insulin, a short-acting insulin analog or analogs, serial and recorded glucose determinations with a handheld meter, and daily review and adjustment of the insulin doses used based on the values obtained, taking into account other confounding factors, such as patient improvement or deterioration in overall condition, oral eating status, concomitant medications, and insulin sensitivity. Basic recommendations for the institution and titration of insulin dosing paradigms in patients who are not perioperative or immediately postoperative are illustrated in Tables 1 through 3 and Figure 13.

**Perioperative and Postoperative Patients and Intensive-Care-Unit Management**

In relatively stable patients on a regimen of basal-bolus insulin with insulin analogs, an anticipated operative time of less than 2 hours, and an anticipated brief postanesthesia-care-unit stay, the following is an updated version of a time-honored set of guidelines that take into account the use of both older and newer insulin preparations:

- If NPH is used as the long-acting insulin, give the normal bedtime dose the night before surgery, and decrease the morning dose of NPH by 50%.
- If insulin glargine is used, decrease the dose by 20% to 30% the night before surgery.
- Withhold the short-acting insulin on the day of surgery.
- Institute either the night before surgery or on call to the operating room an intravenous line containing 5% dextrose (in water) at a low rate of infusion (~20 to 30 mL/h).

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Figure 10. Superimposition of action profiles of insulin lispro and insulin glargine on normal endogenous insulin secretion during the course of 24 hours demonstrating very good overlap onto normal physiologic insulin changes in the nondiabetic patient.

Figure 11. Chemical structure of insulin aspart.

Figure 12. “Roller-coaster” effect of omission of standing basal insulin doses in patients hospitalized with diabetes mellitus who are treated with sliding-scale short-acting insulin only.
Perform perioperative and intraoperative capillary glucose measurement at least every 2 hours during operative and anesthesia time. Once the patient is back on his or her regular medical or surgical floor, the previously established diabetes treatment paradigm can be reinstituted, ie, basal insulin is continued, and short-acting insulin administration is restarted when the patient is able to eat.

Long Operative Times and Compromised Patients

For the following types of patients, preoperative institution of continuous intravenous insulin infusion should be used to control blood glucose levels:

- Patients with considerably longer operative times (>4 hours)

| Table 1. Calculation of Initial Insulin Dose Based on the Body Mass Index (BMI) |
|---------------------------------|-----------------------------|
| Situation                        | Example                     |
| Type 1 diabetes mellitus, average weight or cachectic | 0.5–0.6 U/kg per day 55% basal, 45% bolus |
| Type 2 diabetes mellitus, obese, BMI 28–35 | 0.8–1.0 U/kg per day 60% basal, 40% bolus |
| Super-obese (BMI >35), with or without type 2 diabetes mellitus | 1.2–1.5 U/kg per day 65% basal, 35% bolus |

Note: Body mass index is calculated as weight in kilograms divided by the square of the height in meters.

| Table 2. Calculation of Additional Insulin Doses Based on Severity of Illness |
|---------------------------------|-----------------------------|
| Situation                        | Example                     |
| Mildly ill, anorexic            | +0.0 U/kg per day          |
| Mildly ill, eating              | +0.1 to +0.2 U/kg per day  |
| Moderately ill                  | +0.2 to +0.4 U/kg per day  |
| Severely ill                    | +0.5 to +0.7 U/kg per day  |

Note: (add to base requirements)

- Patients with predicted extended postanesthesia-care-unit stays or expected postoperative transfer to the intensive-care unit
- American Society of Anesthesiologists’ class III or higher patients
- Patients with previously unstable glucose control
- Patients taking oral agents alone with previously fair-to-good glucose control that has deteriorated after removal of those agents in the hospital
- Patients with diabetes mellitus undergoing emergency surgery

Continuous intravenous insulin infusion can be prepared by using 100 to 250 U of insulin lispro (or regular insulin) in 100 to 250 mL of 5% dextrose (in water) on a motorized intravenous pump to give an end concentration of 0.25 to 1.0 U per milliliter of fluid, infused initially at a rate of 1 U/h, accompanied by an infusion of 5% dextrose (in water) in a separate intravenous line at 100 mL/h, fluid status permitting. Finger-stick glucose determinations should be per-

| Table 3. Choice of Which Ongoing Insulin Dose to Change Based on Current Finger-stick Glucose Determination |
|---------------------------------------------------------------|---------------------------------------------|
| If This Glucose Level Is High | Adjust This Insulin Dose                     |
| Fasting blood sugar                                      | Bedtime insulin glargine/NPH insulin        |
| Postprandial breakfast or before lunch value              | Breakfast short-acting insulin              |
| Postprandial lunch or before supper value                 | Lunch short-acting insulin                  |
| Postprandial supper or bedtime value                      | Supper short-acting insulin                 |

A) Calculate BMI:
\[\text{BMI} = \frac{\text{wtlbs}}{\text{htin}^2} \times 703\]
\[= \frac{[145/(60 \times 60)]}{703}\]
\[= 0.04 \times 703 = \text{BMI} 28\]

B) Initial Insulin Dose Calculations:
\[\text{Obese (0.8–1.0) + Moderately ill (0.2–0.4)} = -1.2–1.4 \text{ U/day}\]
\[\text{Total Insulin Dose} = \text{BMI} \times \text{U/day}\]
\[= 28 \times 1.4 = 39.2 \text{ (round to 40) U/day}\]

C) Insulin Division:
\[60\% \text{ basal, } 40\% \text{ bolus}\]
\[= 0.6 \times 40 = 24 \text{ U glargine (basal) at bedtime}\]
\[= 0.4 \times 40 = 16 \text{ U lispro (bolus)}\]

D) Lispro Distribution (roughly 40%, 20%, 40% to start)
\[= 6 \text{ U lispro at breakfast, 4 U at lunch, 6 U at supper}\]
formed no less frequently than every 2 hours while awake in these patients, and every 1 hour of anesthesia plus operative time. Once the patient is back in the intensive-care unit, and depending on the patient’s stability, postoperative performance of finger-stick glucose determinations can be as infrequent as every 4 hours or as frequent as every 30 min in patients deemed continuously unstable. The goal is to keep the blood glucose level between 100 and 150 mg/dL in an ongoing fashion. Titration of the continuous intravenous insulin infusion against the patient’s finger-stick glucose levels can be accomplished by initially calculating the approximate 24-hour insulin requirement in the manner outlined in Tables 1 through 3, dividing the value by 24, and starting an intravenous insulin infusion at that rate (in units per hour). Subsequent adjustments to and management of the insulin drip can be performed as outlined in Tables 4 and 5.

In removing an insulin infusion from a patient, generally one should consider injecting at least 60% of the patient’s normal basal (long-acting) insulin dosage subcutaneously at least 60 to 90 min before discontinuation of the continuous intravenous insulin infusion since the latter allows for no depot reservoir of subcutaneous insulin and since the half-life of intravenous insulin is measured in minutes. Rebound hyperglycemia, the most common compromising morbid event associated with the discontinuation of continuous intravenous insulin infusion, can occur if this recommendation is not followed. In addition, if the patient can take substantial nourishment orally, then the usual short-acting insulin dose associated with that meal should also be administered approximately 60 to 90 min before discontinuation of the continuous intravenous insulin infusion. A simplified pathway to follow the previous recommendations is demonstrated in Figure 14. The active involvement of a general medical specialist or endocrinologist can be very helpful.

### Special Situations

**Continuous Subcutaneous Insulin Infusion: Insulin Pumps**

Patients with type 1 diabetes mellitus who use insulin pumps are generally well informed about all of the nuances of the functioning of their device, as is the endocrinologist helping to care for these patients. While awake, alert, and not compromised by psychoactive agents, preoperative sedation, pain medication, and so on or by the primary reason for hospitalization, these patients are likely to be responsive to, and helpful with, dosage adjustments asked of them based on finger-stick glucose levels obtained in the hospital. However, when rapid decisions must be made regarding glucose control or the patient is compromised, health-care staff may not be able to

### Table 4. Choice of How Much to Adjust the Standing Order for Any Given Insulin Dose Based on Finger-stick Glucose Levels

<table>
<thead>
<tr>
<th>Glucose Level (mg/dL)</th>
<th>Change in Next Insulin Dose</th>
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<tbody>
<tr>
<td>0–80</td>
<td>↓10%</td>
</tr>
<tr>
<td>81–200 (80–150 ICU)</td>
<td>No change</td>
</tr>
<tr>
<td>201–250 (151–200 ICU)</td>
<td>↑10%</td>
</tr>
<tr>
<td>251–300 (201–250 ICU)</td>
<td>↑20%</td>
</tr>
<tr>
<td>301–350 (251–300 ICU)</td>
<td>↑40%</td>
</tr>
<tr>
<td>351–400 (301–350 ICU)</td>
<td>↑60%</td>
</tr>
</tbody>
</table>

Abbreviation: ICU, intensive-care unit.

### Table 5. Guidelines for Treating the Current/Out-of-Acceptable-Range Glucose Level

<table>
<thead>
<tr>
<th>Glucose Level (mg/dL)</th>
<th>Absolute</th>
<th>Relative</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–50 or symptomatic</td>
<td>½ A 50% dextrose (in water) intravenous push, retest in 15 min</td>
<td>10% addition to base dose</td>
</tr>
<tr>
<td>51–80</td>
<td>15–30 g carbohydrate</td>
<td>20% addition to base dose</td>
</tr>
<tr>
<td>81–200 (80–150 ICU)</td>
<td>No change</td>
<td>40% addition to base dose</td>
</tr>
<tr>
<td>201–250 (151–200 ICU)</td>
<td>Additional 3 U of lispro</td>
<td>50%–80% addition to base dose, consider continuous intravenous insulin infusion if very ill</td>
</tr>
<tr>
<td>251–300 (201–250 ICU)</td>
<td>Additional 6 U of lispro</td>
<td></td>
</tr>
<tr>
<td>301–350</td>
<td>Additional 10 U of lispro</td>
<td></td>
</tr>
<tr>
<td>351–400</td>
<td>Additional 15 U of lispro, consider continuous intravenous insulin infusion if very ill</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: ICU, intensive-care unit.

Note: Use simultaneously with Tables 3 and 4 for calculation of ongoing insulin doses.
accurately adjust the rate of insulin infusion that an insulin pump provides. For this reason, in patients whose hospital stay is expected not to be complicated by a change in mental status owing to medication or infirmity from their disease, continued use of the pump with repeated contact with the patient’s endocrinologist through the nursing staff is generally acceptable. If complications are considered likely, then it is best to calculate a basal-bolus dosing paradigm and use subcutaneous insulin or switch to continuous intravenous insulin infusion. Regardless of the option chosen, ideally it should be instituted at least 60 min before the physical removal of the infusion cannula of the patient’s insulin pump from the subcutaneous tissue. On hospital discharge, the patient can restart the pump.

Continuous Enteral Feedings or Total Parenteral Nutrition

For patients receiving enteral feeding, a continuous total parenteral nutrition regimen is preferable because it allows the use of a flat insulin analog, such as insulin glargine, given in two divided doses exactly 12 hours apart. Because both the feeding rate and the diffusion rate of the insulin into the bloodstream are essentially “flat and steady,” excellent control of blood glucose levels can be expected.51

Total parenteral nutrition, for patients who require it, is commonly accompanied by the addition of regular insulin to the admixture, calculating the number of units required by taking into account the patient’s glucose levels during the past 24 hours, body weight, calorie type and number infused, and so on. In the known diabetic patient, however, exaggerated hyperglycemic swings in response to high concentrations of infused dextrose or lipids (type 1 and type 2 diabetes) or the potential for the precipitation of a hyperosmolar state (type 2 diabetes) or diabetic ketoacidotic state (type 1 diabetes) is possible.

In addition, and because of these concerns, one should a priori expect to use between 15% (type 1 diabetes) and 50% (type 2 diabetes) more insulin per infused calorie during the infusion of total parenteral nutrition in a patient with diabetes and should be prepared to inject supplemental subcutaneous in-

Figure 14. Simplified pathway for the initial care of a patient with diabetes mellitus who is hospitalized. ASA, American Society of Anesthesiologists; DM, diabetes mellitus; ICU, intensive-care unit; IV, intravenous.
insulin in response to finger-stick glucose determinations made every 6 hours or four times daily, just as with hyperglycemia under any other circumstances. Again, the active involvement of a general medical specialist or endocrinologist can be very useful.

Conclusion

Patients admitted to the hospital, whether they are subjected to operative intervention or not, are more likely to be diabetic than the average outpatient. Among inpatients, those who have diabetes mellitus are more likely to have longer hospital stays, more morbid events, and less desirable outcomes. In the near future, many more patients are expected to suffer from diabetes mellitus. New and emerging studies suggest that the outcomes of patients hospitalized with diabetes mellitus are significantly affected by the level of acute glycemic control obtained while the patient is hospitalized and that this acute glycemic control has implications separate from considerations of long-term outpatient control.

This level of acute glycemic control and its effects on morbidity and mortality extend not only to the patient known to have diabetes mellitus but also to all patients experiencing hyperglycemia while hospitalized. Older methods for ascertaining and treating levels of glycemia are rapidly giving way to the new: newer glucose meters, newer insulin analogs, and, most important, a newer approach to what constitutes “good glucose control.”

Most oral agents used in the outpatient treatment of diabetes mellitus are either unhelpful or potentially dangerous in the hospitalized diabetic patient, with the most problematic one being metformin. Therefore, for most inpatients, at least a temporary changeover to insulin therapy is generally recommended. The use of newer insulin analogs, with more sharply defined and physiologically appropriate action profiles, has made the achievement of inpatient control of glycemia safer and easier, as has the availability of better, faster, and smarter glucose meters. In special situations, such as the unstable or severely ill patient, the high-risk preoperative surgical patient, and the patient receiving total parenteral nutrition, an insulin infusion is the treatment of choice.

The first part of the 21st century holds great promise for improving the health and survival of the hospitalized patient with diabetes mellitus, as the end of the 20th century foretold for the outpatient with diabetes. Physicians seek to take advantage of this new and emerging information to improve the lives of our inpatients with diabetes.

References


44. HUMALOG [prescribing information], Eli Lilly and Co, Indianapolis, August 2000.

45. LANUS [prescribing information], Aventis Pharmaceuticals, Kansas City, MO, May 2003.


