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Better glycemic control in the hospital: Beneficial and feasible

ABSTRACT

Hospitalized patients fare better if their blood glucose levels are strictly controlled. To manage blood glucose effectively, hospitals need to set up formal programs. Attending physicians, endocrinologists, and nurses need to work as a team. Standardized forms with management guidelines are valuable.

KEY POINTS

In consensus guidelines, the goal fasting plasma glucose level in patients not in an intensive care unit is less than 130 mg/dL, and the goal maximal level is less than 180 mg/dL. For patients in intensive care, the goal is less than 110 mg/dL.

If used by itself, "sliding scale" management can lead to dangerous swings in blood glucose levels.

Effective insulin therapy consists of three components: basal (daily or twice-daily injections of long-acting insulin or continuous infusions of regular insulin), prandial or nutritional (injections of rapid-acting insulin before meals), and correctional (using a sliding scale).

A comprehensive review of this topic is available in *Diabetes Care* 2004; 27:553–591.

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ALTHOUGH many hospitalized patients have hyperglycemia, physicians traditionally tend to look the other way, believing that it is better to "do no harm," ie, to allow blood glucose levels to run a little on the high side rather than risk causing hypoglycemia with too-aggressive insulin therapy.

But short-term outcomes—including in-hospital death rates and the incidence of hypoglycemia—are better if blood glucose levels are carefully and systematically controlled. Therefore, professional societies have issued consensus guidelines urging hospitals to tackle hyperglycemia in an organized fashion, and hospitals are taking up the challenge.

HYPERGLYCEMIA IS COMMON AND HARMFUL

An estimated 20 million people in the United States are known to have diabetes, and another 40 million or so have impaired glucose tolerance. Still another substantial group has undetected diabetes or impaired glucose tolerance. In addition, under the physiological stress induced by hospitalization, many patients with borderline hyperglycemia enter the diabetic range.

In a community hospital

Umpierrez et al[1] reviewed the blood glucose levels of 2,030 consecutive patients and found that 38% had hyperglycemia at the time of admission (defined as having either fasting blood glucose ≥ 126 mg/dL or two determinations of random blood glucose ≥ 200 mg/dL). Almost one third of those with hyperglycemia had no known history of diabetes before admission.

The in-hospital death rate was 16% in the patients with newly discovered (and therefore untreated) hyperglycemia, compared with 3% in those with a known history of diabetes and 1.7% in those with normal blood glucose ($P < .01$ for both comparisons). One could argue that the patients with higher glucose levels were more likely to die because they were sicker to begin with. However, the same trends were apparent when patients who were immediately admitted to intensive care at the time of admission were excluded from the analysis: the death rate was 10.0% in patients with previously unrecognized hyperglycemia, 1.7% in those with known diabetes, and 0.8% in those with normal blood sugar levels ($P < .01$ for both comparisons). The patients with newly discovered hyperglycemia and known diabetes actually had similar blood sugar levels at the time of admission.

Patients with newly discovered hyperglycemia stayed in the hospital for a mean of 9 days, compared with 5.5 days for patients with known diabetes and 4.5 days for patients with normoglycemia ($P < .01$ for both comparisons). Twenty-nine percent of the patients with newly discovered hyperglycemia were admitted to the intensive care unit, compared with 14% of patients with known diabetes and 9% of patients with normoglycemia ($P < .01$ for both comparisons). In addition, patients with newly discovered hyperglycemia were less likely to be discharged home and were more likely to be discharged to a nursing home or other long-term care facility.

Untreated hyperglycemia causes many bad outcomes in the hospital

Poorer outcomes in patients with hyperglycemia have also been noted in a number of specific medical settings:

In renal transplant recipients

Thomas et al[2] assessed blood glucose levels in 50 consecutive patients with known diabetes during the first 100 hours after renal transplantation and found that 58% of patients with a mean blood glucose level of 200 mg/dL or higher had rejection episodes, compared with only 11% of patients with blood glucose levels less than 200 mg/dL. The average difference in blood sugar levels in patients with a rejection episode vs those with no rejection episode was only 50 mg/dL.

In elective surgical patients

Pomposelli et al[3] monitored glucose control in diabetic patients undergoing elective surgery. Patients with glucose levels higher than 220 mg/dL on the day after surgery had 2.7 times more nosocomial infections on the first postoperative day than patients with lower levels. When minor infections of the urinary tract were excluded from analysis, the infection rate was 5.7 times higher in patients with poor glucose control. Preoperative and second-day postoperative blood sugar levels were found to be less important in predicting the infection rate.

In cardiac surgical patients

Furnary et al[4] analyzed the outcomes of 2,467 patients with diabetes who underwent open heart surgery over a 10-year period. During the first years, patients received subcutaneous insulin injections on a sliding scale, and the incidence of deep sternal wound infection was 2.0%. In later years, they received continuous intravenous insulin infusions with the goal of keeping blood glucose levels lower than 200 mg/dL, and the incidence of deep sternal wound infection was 0.8% ($P = .01$ by chi-square test), a rate similar to that in patients without diabetes.

Strict glucose control was also associated with dramatically lower hospital death rates: 14.5% of patients died who had average postoperative blood glucose levels above 250 mg/dL, compared with 0.9% of patients with levels below 150 mg/dL.[5] Most deaths were due to cardiovascular events.

In intensive care patients

Van den Berghe et al[6] randomly assigned 1,548 patients admitted to surgical intensive care who received mechanical ventilation to receive either intensive insulin therapy (with blood glucose maintained between 80 and 110 mg/dL) or conventional treatment (in which insulin infusions were given only if blood glucose exceeded 215 mg/dL). The average morning blood sugar level in the tightly controlled group was 103 mg/dL, compared with 153 mg/dL in the conventionally treated group. Forty-two percent fewer patients who received intensive therapy died in the hospital. The incidence of sepsis was also significantly lower, as was the need for dialysis, blood

transfusions, or ventilation support for longer than 14 days.

However, a similar study of patients in a medical intensive care unit did not find a significantly lower death rate with intensive therapy than with conventional insulin therapy.[7] The rate was modestly lower with intensive therapy in the subgroup who stayed longer than 3 days, but this information may not be clinically useful because length of stay is not always predictable at the time of admission. Nevertheless, patients on intensive therapy had a lower incidence of new kidney injury, shorter time on mechanical ventilation, and shorter length of stay in the intensive care unit and the hospital.

WHY DOES HYPERGLYCEMIA CAUSE BAD OUTCOMES?

Hospitalized patients are under significant metabolic stress. Stress hormones, including growth hormone, cortisol, and epinephrine, are elevated, causing blood glucose levels to rise. If patients have impaired glucose metabolism to begin with, their blood sugar levels are liable to rise into the diabetic range in the hospital.

In a vicious circle, blood sugar levels higher than 200 mg/dL actually suppress beta cells

In a vicious circle of glucose toxicity, blood sugar levels higher than 200 mg/dL actually suppress beta cell function, so that less insulin is secreted and glucose levels climb even further. Although this effect is counterintuitive, it has been well demonstrated in animals.[8]

Evidence of glucose toxicity also exists in people: patients with a genetic tendency towards type 2 diabetes may develop diabetic ketoacidosis, but after being treated aggressively in the hospital, they can often return home without being maintained on insulin therapy.

Hyperglycemia is harmful for several reasons:

Enhanced tissue injury. Once a hyperglycemic cycle starts, the body goes into a catabolic state, signaling the liver and fat to release free fatty acids and ketones and to increase lactate production to create alternative fuels for extra energy. While a healthy person can cope with such conditions, sick patients with ischemic or infected tissue sustain additional direct tissue injury from the alternative fuels.

Lowered immune resistance. Blood sugar levels higher than 180 mg/dL inhibit neutrophils so that they are less able to migrate to areas of infection and to adhere to bacteria and kill them. Antibiotics only buy time until neutrophils and the rest of the immune system rebound. If the immune system cannot rally, resistant organisms take over.

Increased inflammation. Nitric oxide levels are lower in hyperglycemia, leading to higher levels of reactive oxygen species, transcription factors, and other secondary mediators such as inflammatory cytokines, tissue necrosis factor, interleukins, C-reactive protein, and nuclear factor kappa B, which exert direct cytotoxic effects.

Platelet aggregation. Shechter et al[9] observed platelet aggregation using inverted porcine aortas in a perfusion chamber and exposing them to flowing venous blood from patients with coronary artery disease who were fasting and taking full-dose aspirin therapy. Platelets aggregated significantly more in the blood from patients with elevated blood glucose levels, regardless of serum cholesterol levels, blood pressure, and smoking status.

NEW GLUCOSE GOALS FOR HOSPITALIZED PATIENTS

In view of these data, the American Diabetes Association, the American Association of Clinical Endocrinologists, and other specialty groups developed consensus guidelines for hyperglycemia control in hospitalized patients.[10,11] Goals:

- For patients not in an intensive care unit, fasting blood glucose less than 100 mg/dL, maximal blood glucose less than 180 mg/dL
- For patients in an intensive care unit, less than 110 mg/dL.

BARRIERS TO BETTER CONTROL

'Do no harm'

Some doctors are reluctant to comply with the new stricter targets for fear that aggressive therapy will lead to hypoglycemia. Indeed, profound hypoglycemia is a dramatic event, whereas hyperglycemia does not obviously manifest itself.

Furthermore, many doctors regard managing hyperglycemia as an extra chore, and they

ignore it unless patients are specifically admitted with diabetic ketoacidosis or in a hyperosmolar coma. On the average, today's patients are sicker than in the past, and managing infections, illnesses, and procedures tends to take precedence.

Hyperglycemia in hospitalized patients is also challenging to manage. Patients may be on "nothing by mouth" (NPO) status for long periods and so are more prone to develop hypoglycemia. Inactivity exacerbates blood glucose control, as does the often unappetizing food, which may be served at erratic times with no regard to the patient's insulin schedule.

Insulin can be difficult to administer safely

Insulin is the primary treatment for hyperglycemia in the hospital. Oral agents do not work well and are often contraindicated in hospitalized patients.

However, insulin therapy must be managed carefully. Several problems are associated with insulin therapy.

High error rate. Insulin is on the Institute for Safe Medication Practices' list of drugs with an increased risk of causing significant harm when used in error. Errors in insulin orders or administration commonly arise in hospitals, causing diabetic ketoacidosis from lack of basal insulin (see below), or on the other extreme, severe hypoglycemia because of errors in dosage or from "insulin stacking." (Stacking occurs when regular insulin is given at regular 4-hour intervals throughout the day. Although regular insulin is considered to be rapid-acting, it can be active for as long as 8 hours. Each subsequent dose has the effect of "stacking" onto the previous doses, causing severe hypoglycemia by the second or third dose.)

Another opportunity for error comes from the names of the preparations—for example, Lantus (glargine, which is long-acting) and lispro (Humalog, which is short-acting).

Inconsistent guidelines. Current practices vary, and no standard guidelines for insulin therapy have existed until very recently. At teaching hospitals, each new medical resident tends to arrive with a different sliding scale of insulin therapy that he or she learned in medical school. Numerous guidelines are especially difficult for nursing staff to contend with.

What's wrong with the sliding scale?

The traditional sliding scale involved measuring the patient's blood glucose level (or, long ago, the urine glucose level) before each insulin dose and giving a higher dose if the glucose level was high. The concept is good, but a sliding scale scheme by itself cannot keep blood sugars consistently in the target range and can be dangerous in an insulin-deficient patient. It is retroactive, responding to blood glucose levels rather than anticipating them, and it frequently causes a harmful roller-coaster effect. Furthermore, sliding scales were never standardized, so every physician used his or her favorite formula.

Queale et al[12] monitored blood glucose levels in 171 consecutive hospitalized patients with diabetes and found that 23% experienced hypoglycemic episodes and 40% experienced hyperglycemic episodes. Seventy-six percent of the patients were on sliding scale insulin regimens, and they had a rate of hyperglycemic episodes three times higher than that in patients on no pharmacologic regimen.

A COMPREHENSIVE APPROACH TO INSULIN THERAPY

A more physiologic approach to insulin replacement has three components: basal insulin, nutritional insulin, and correction insulin (TABLE 1).

Regular insulin can be active for as long as 8 hours, leading to a 'stacking' effect

Basal insulin is the amount of exogenous insulin required to maintain blood sugar levels when not eating, ie, between meals and at night. Without basal insulin, blood glucose levels rise by about 45 mg/dL per hour in patients who are insulin-deficient, and ketone production starts almost at once.[13,14]

Basal insulin is provided as an injection of a long-acting insulin—eg, insulin glargine (Lantus) once a day at bedtime or in the morning—or as an intravenous insulin drip. Other alternatives are neutral protamine Hagedorn (NPH) or lente twice a day, but I do not recommend them, as they both have peaks in their actions, whereas glargine does not.[10]

All patients who are truly insulin-deficient should receive basal insulin. True insulin deficiency can be identified by any one of the following characteristics (which we list on a laminated pocket card that we give to every intern):

TABLE 1

Practical guidelines for insulin therapy for hospitalized patients

If the patient is eating

Basal	Glargine (Lantus) once a day at bedtime or in the morning; or Neutral protamine Hagedorn (NPH) or lente twice a day, in the morning and at bedtime (not recommended); or Insulin drip
Nutritional	Aspart (NovoLog) or lispro (Humalog) up to 15 minutes before meals; or Regular insulin 30 minutes before meals (not recommended)
Correction	Aspart or lispro up to 15 minutes before meals (see TABLE 2)

If the patient is receiving perioperative care (receiving nothing by mouth)

Basal	Insulin drip; or Regular insulin every 4–6 hours; or Aspart or lispro every 4 hours; or Glargine (give usual daily dose); or Neutral protamine Hagedorn (NPH) (give half the usual morning dose)
Nutritional	Not applicable, or per guidelines for total parenteral nutrition or enteral feeding
Correction	Regular insulin every 4–6 hours; or Aspart or lispro every 4 hours

If the patient is receiving total parenteral nutrition

Basal	Glargine
Nutritional	Regular insulin added to TPN bag
Correction	Aspart, lispro, or regular insulin every 4–6 hours

If the patient is receiving enteral nutrition

Basal	Glargine once a day at bedtime or in the morning; or NPH twice a day
Nutritional	If receiving continuous feeding, aspart or lispro insulin every 4 hours or regular insulin every 4–6 hours If receiving bolus feedings, aspart or lispro, or regular insulin with feedings
Correction	Aspart or lispro every 4–6 hours or regular insulin every 4–6 hours

Without basal insulin, blood glucose levels rise by about 45 mg/dL/hour

TABLE 2

Calculating supplemental (correction) insulin doses

FINGER-STICK BLOOD GLUCOSE (MG/DL)*	ADDITIONAL UNITS OF RAPID-ACTING INSULIN TO GIVE†		
	PATIENTS NEEDING ≤ 40 UNITS/DAY	PATIENTS NEEDING 40–80 UNITS/DAY	PATIENTS NEEDING > 80 UNITS/DAY
121–199	1	1	2
200–249	2	3	4
250–299	3	5	7
300–349	4	7	10
> 349	5	8	12

*Measured before meals and at bedtime, or every 4 or 6 hours for intensive care patients or those on tube feeding
†Give half this amount if at bedtime

- Known type 1 diabetes mellitus
- History of pancreatectomy or pancreatic dysfunction
- History of wide blood glucose fluctuations
- History of ketoacidosis
- History of insulin use for more than 5 years.

Nutritional insulin is the amount of insulin needed to cover food intake, intravenous dextrose, total parenteral nutrition, enteral tube feedings, and nutritional supplements. Nutritional insulin needs are provided with regular insulin 30 minutes before meals or, preferably, with rapid-acting insulin aspart (NovoLog) or lispro (Humalog) up to 15 minutes before meals.

Supplemental insulin (also known as "correction" insulin) is the amount of insulin given for unexpected hyperglycemia. This concept is similar to the old sliding scale method, but it should only be a relatively small part of blood glucose management. Supplemental insulin is provided with regular or rapid-acting insulin with meals (TABLE 2). To minimize the risk of nocturnal hypoglycemia, rapid-acting and regular insulin should not be given at bedtime.

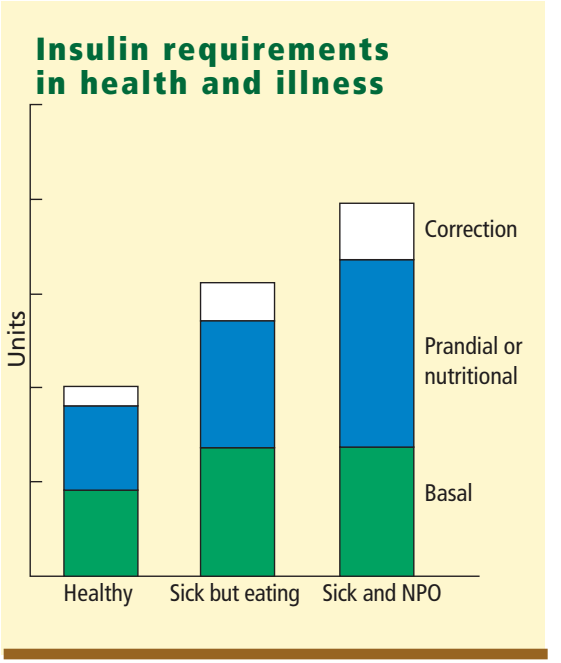

FIGURE 1. Components of insulin requirement are divided into basal, prandial or nutritional, and correction insulin. When writing insulin orders, the basal and the prandial or nutritional insulin doses are written as programmed (scheduled) insulin, and correction insulin is given according to an algorithm to supplement the scheduled insulin (see TABLE 2). Programmed and correction insulin are increased to meet the higher daily basal and prandial or nutritional requirements. Total insulin requirements may vary widely.

Supplemental insulin should be only a small part of glucose management

PRACTICAL GUIDELINES FOR INSULIN REGIMENS

For hospitalized patients, insulin needs tend to vary widely and can be expected to change with the clinical condition. A sick patient should never be taken off insulin for not eating: such patients actually have high basal and total insulin needs. As a patient's condition and food intake improve, the nutritional component increases, and the basal and correction doses often diminish (FIGURE 1).[10]

Insulin regimens must be individualized, but certain practical guidelines can be followed (TABLE 1). Special circumstances alter standard insulin needs in hospitalized patients, and allowances must be made for control during the perioperative period for patients on enteral or parenteral nutrition and during treatment with glucocorticoids.

Starting insulin treatment

For a hospitalized patient with insulin deficiency, we usually start with insulin glargine 0.4 units/kg per day for basal coverage, or 0.3 units/kg/day in patients at high risk of hypoglycemia (elderly patients or those with renal, cardiac, or hepatic dysfunction). Prandial or nutritional coverage can be provided with insulin aspart or insulin lispro 0.1 unit/kg either before or after each meal.

If the patient is eating, we measure blood glucose with a finger-stick before each meal and at bedtime and give correctional doses of aspart or lispro depending on the patient's glucose level and on his or her total insulin dose (TABLE 2).

For preoperative and perioperative patients

Dosage correction

Basal insulin is essential during the preoperative and perioperative periods. For prolonged NPO status, insulin drip is preferred, with a starting dose of 0.02 units/kg/hour perioperatively. Nutritional insulin may not be needed, but a correction dose may be needed until the patient resumes eating.

For patients receiving enteral nutrition

No good studies exist on the best insulin therapy for patients receiving enteral nutrition. For patients on a continuous enteral regimen, we give aspart, lispro, or regular insulin every 4 to 6 hours with or without basal insulin. For those receiving a bolus enteral regimen, we usually give subcutaneous regular insulin before each bolus.

For patients receiving total parenteral nutrition

To determine a patient's daily insulin requirement, a separate insulin infusion (aspart, lispro, or regular) should be used for 24 hours. Thereafter, 60% to 80% of the 24-hour insulin requirement can be added to the total parenteral nutrition bags to meet basal and nutritional insulin needs, and supplemental insulin can be provided every 4 to 6 hours as needed. Subcutaneous insulin should only be used with caution to avoid erratic blood glucose control.

Nurses are key players in managing blood glucose in the hospital

Transition from intravenous to subcutaneous insulin

To minimize rebound hyperglycemia or "hyperglycemic escape," doses of intravenous and subcutaneous insulin should overlap for at least 4 hours when changing from intravenous to subcutaneous insulin. The prandial insulin can be started while the insulin drip is running. A dose of subcutaneous basal insulin can be given as early as 24 hours before stopping the insulin infusion. Most insulin infusion protocols will cut off when the blood glucose drops below a level of 70 mg/dL. This is a signal that the drip can be safely discontinued.

IMPLEMENTING CHANGE

Georgetown University Hospital has developed initiatives over the past few years to improve glycemic control in hospitalized patients. We have done this, for the most part, without added funding, spearheaded by a team of a physician who serves as a "champion" for the patient, a primary nurse practitioner who serves as the educator, and key nurses, pharmacists, and administrators. Funding a dedicated nurse practitioner (who can write insulin orders) and perhaps a part-time endocrinologist can be useful, especially in a large hospital.

Education is key

We provide in-service training of all doctors and nurses on proper basal and bolus insulin therapy, and we give them laminated cards for reference.

Physicians should be made aware of the impact of blood glucose levels on hospital outcomes, and hospital targets should be set for control. The system of basal, nutritional, and supplemental insulin components for blood sugar control should be understood and used.

Education in hypoglycemia prevention and treatment is essential. Treatment for patients under special circumstances should also be addressed.

Nurses must know how to administer insulin and the optimal timing of subcutaneous insulin injections. They should know how to monitor glucose at the bedside and how to document it, what the critical and target blood glucose levels are, and when to alert the physician.

Nurses are key players in helping to avoid hypoglycemia if they are well trained and use a proactive approach. They should monitor blood sugar levels hourly if hypoglycemia is anticipated, be aware of trends, and adjust insulin therapy, especially by reducing dose of prandial and basal insulins and administering dextrose if needed. They should be able to predict and handle problems if a patient misses a meal, if tube feeding is discontinued, or if a morning procedure is scheduled. For a patient undergoing a lengthy procedure, the nurse should hand off glucose control to the nurse who will care for the patient during the procedure.

Patients. If a hospitalized patient has never been diagnosed with diabetes, he or

she may well resist starting a new therapy. Educational brochures developed by the hospital or a pharmaceutical company can be very helpful. Educational materials should include an explanation of diabetes, the signs and symptoms of both high and low blood sugar, and how to treat hypoglycemia. The patient should understand his or her discharge regimen, how to monitor and record his or her glucose levels, and when to call the doctor.

Standardized forms and guidelines

We developed a standardized order form, a nursing flow sheet, and an intravenous insulin protocol for use outside the intensive care unit. Every component of insulin ordering is included on a single sheet, and freestanding insulin orders are no longer allowed throughout the hospital.

We also eliminated the use of regular insulin except for enteral feeding and insulin drips. Intravenous drip changes and subcutaneous insulin injections require two nurses to check the dosage and sign the orders.

The numerous insulin formulations that are available are often confusing, as very different ones look and sound alike. Reducing the formulary down to a very small number of options is very effective.

A team approach for the care of patients with diabetes is emphasized and involves the attending physician, an endocrinologist, a nurse educator, a dietitian, and a pharmacist. Much is now known about managing hyperglycemia effectively, and building relationships with colleagues can help ensure that errors and problems are avoided.

A strong quality control program is essential for monitoring glucose levels at the bedside. Some monitors give falsely elevated readings, particularly for very sick patients, such as those with shock, hypoxia, dehydration, an extremely abnormal hematocrit, or elevated bilirubin or triglyceride levels, or those taking certain medications. If in doubt, we recommend obtaining paired samples and checking the bedside monitor's value against the laboratory's value.

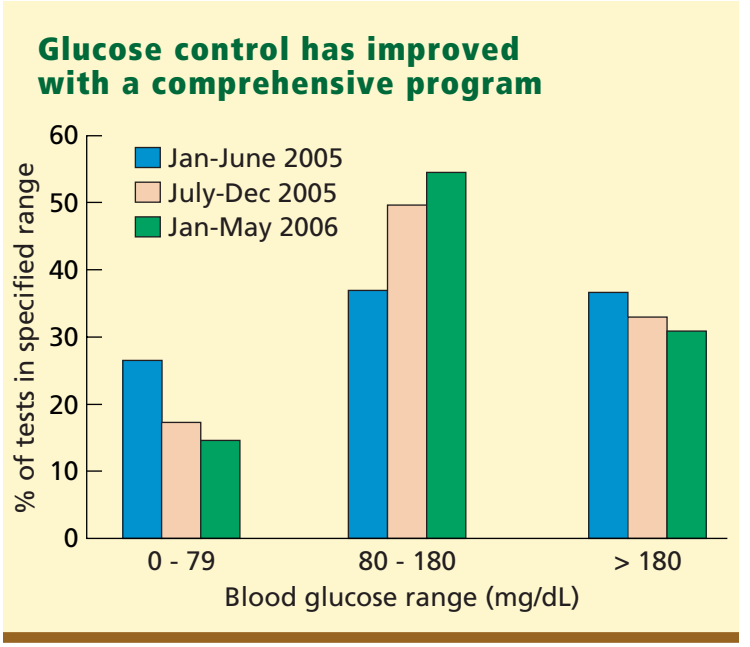

FIGURE 2. Blood glucose levels at Georgetown University Hospital improved after a comprehensive program for controlling inpatient blood glucose levels was implemented in 2004.

Tangible results

Since we implemented a comprehensive glucose program at Georgetown University Hospital in 2004, errors in insulin administration have been reduced by 90%. Since 2005, blood glucose testing has increased by 300%. At the same time, the frequency of hypoglycemia has dropped by 45% (FIGURE 2). This change is attributed to the less frequent use of the sliding scale as the sole insulin therapy and increased reliance on programmed insulin. We are currently analyzing data on length of stay, risk of nosocomial infections, and death.

Future initiatives

Future initiatives include determining blood glucose levels in patients with diabetes within 8 hours of hospital admission. Patients with a blood glucose level of over 200 mg/dL are to be checked to see if bedside measurements of blood glucose and hemoglobin A_{1c} levels have been ordered. Patients with two or more blood glucose readings above 300 mg/dL or less than 60 mg/dL will receive an automatic consult by a nurse practitioner trained in diabetes care.

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