Perioperative management of diabetes mellitus:

How should we act on the limited evidence?

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The proportion of US surgical patients who have diabetes is 15% to 20%,[1] and the percentage may be even greater among those undergoing cardiothoracic surgery. Unfortunately, little evidence-based medicine and no prospective randomized controlled trials exist to guide clinicians in effectively reducing perioperative risk in patients with diabetes.

This article discusses preoperative and postoperative considerations in the management of surgical patients with diabetes and uses case studies to explore practical issues in the management of such patients, including the importance of glucose control in preventing postoperative complications, the role of intensive insulin therapy, and insulin dosing strategies. Because good evidence on the perioperative management of diabetes is lacking, much of this discussion is based on our experience at The Cleveland Clinic.

PREOPERATIVE CONSIDERATIONS

Preoperative considerations for the patient with diabetes include the patient's diet, the medications he or she is taking, and the associated complications of diabetes.

Diet

There is no such thing as the "usual diabetic diet." Nutrient status is obviously adequate if patients are freestanding and eating in the preoperative state. Perioperative management of the diet is straightforward and consists of putting patients on a "nothing by mouth" (NPO) order for most procedures. For some this means missing a single meal during the day and for others it means missing several meals, depending on the surgical procedure. Gut procedures, for example, require patients to be NPO for more than 1 day.

Diabetes medications

Insulin. The appropriate strategy for insulin management in a patient with diabetes who is taking insulin should mimic physiologic insulin secretion—ie, a basal plus a calorie-stimulated bolus of insulin. Even if the patient is NPO, basal insulin replacement should be continued. Removing the basal insulin will make diabetes control more difficult from the start.

An appropriate strategy is to use one half to two thirds of the patient's usual insulin dose in the form of an intermediate-acting insulin the evening before and the morning of surgery, with the option to give a full dose. Basal insulin with insulin glargine is fairly stable and generally can be given as a full dose.

Preoperatively, blood glucose levels should be less than 200 mg/dL; higher levels can cause neutrophil dysfunction, compromising bacterial killing. Elevated blood glucose levels can be brought down to 150 mg/dL safely with neutral protamine Hagedorn (NPH) insulin.

Oral diabetes medications should be held on the day of surgery. How to manage metformin administration is somewhat controversial. Based on recommendations in the package insert that metformin should be stopped 48 hours before administration of radiocontrast materials, many physicians stop metformin 48 hours before a surgical procedure. No evidence exists to support this recommendation in patients with normal renal function. If metformin is to be restarted after the procedure, be certain that renal function is normal before doing so. Sulfonylureas and thiazolidinediones can typically be stopped on the morning of surgery.

Diabetes complications

The complications of diabetes must be considered in the preoperative assessment.

Coronary heart disease. The risk of coronary heart disease (CHD) is increased twofold to fivefold in dia-

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betic as opposed to nondiabetic patients, and the risk of CHD conferred by diabetes is greater in women than in men.[2–6] Be aware that diffuse CHD may be present in the absence of symptoms (ie, "silent" CHD). Women with CHD are less likely to present with classic symptoms and have less chest pain, so the threshold for suspicion of CHD needs to be lower in women.

As opposed to the risk factor–based approach that the American Diabetes Association recommends when screening for CHD,[7] which is based on traditional risk factors such as dyslipidemia and hypertension, one of the best predictors of silent myocardial disease is autonomic neuropathy, even in the absence of other cardiovascular risk factors. Therefore, the patient with neuropathy, gastroparesis, and orthostatic hypotension is at increased risk for CHD and should undergo additional screening for CHD. Albuminuria increases the risk of not only renal disease but CHD as well.

Diabetic nephropathy increases substantially the risk of CHD, volume overload, and hyperkalemia, and affects glucose-lowering agents but usually not anesthetic agents.

Peripheral neuropathy is a major contributor to lower extremity infection; in the insensate foot, infection often goes unrecognized. When managing a hospitalized patient with diabetes, remove the patient's bedsheet and look at the heels. It is simple to do but not done as consistently as it should be.

Beta-blocker use

Caution should be exercised in the use of beta-blockers, as the beneficial effects of preoperative beta-blocker use have not been firmly established in patients with diabetes mellitus.

In the Diabetic Postoperative Mortality and Morbidity (DIPOM) trial, a randomized controlled study of 921 patients reported in abstract form,[8] metoprolol started the evening before surgery and continued until discharge was not associated with a reduction in all-cause mortality or adverse cardiac outcomes compared with placebo in patients with diabetes, and there was a nonsignificant trend toward more adverse events in the metoprolol recipients. Heart failure accounted for most of the excess adverse events in the metoprolol group. The message from the DIPOM trial is not to withhold beta-blockers in patients with diabetes but to be attentive that insidious heart failure may be more common with beta-blockade in diabetic patients.

Preoperative instructions

Preoperative written instructions may need to be different for diabetic patients. For instance, many patients with diabetic retinopathy have difficulty with color vision and contrast vision. Preoperative instructions should therefore be printed in black on a white or yellow background, and in at least 14-point type.

POSTOPERATIVE CONSIDERATIONS

Diet/nutritional intake, medications, and complications also need to be considered in the postoperative phase.

Diet

Most patients are NPO at the start of the postoperative period, at least temporarily. Clear liquids that contain no nutrients, even if caloric, probably do not reverse the catabolic state. In general, the diet in the hospital does not have to be very restrictive. The goal is adequate wound healing and nutrition. A diet that does not conform entirely to the recommended outpatient diet is better than not eating at all upon discharge.

Some patients may need nutritional support as total parenteral nutrition (TPN) or enteral nutrition (tube feedings). Tube feedings are usually given continuously over 24 hours at a fixed rate. However, if the tube feeding is likely to be needed after discharge, then feedings may be given intermittently. Often such feedings are given overnight (eg, from 6:00 PM to 6:00 AM); patients are encouraged to eat during the day. The transition from continuous to intermittent (nighttime) feeding is difficult. For a patient who will be recommended for a switch from continuous to nighttime enteral feeding, making that change a couple of days before discharge will provide time to make adjustments in the insulin administration schedule.

Insulin

Postoperative insulin needs can be estimated by preoperative insulin requirements. As a general rule, half the preoperative insulin requirement can be given as a basal dose. For example, if the patient had been taking 100 U/day, he or she can be moved up to 50 U of basal insulin very quickly, even if he or she is NPO.

The postoperative insulin requirement is also dependent on nutrient intake. When making rounds in the morning, I ask patients, "What did you eat yesterday and how well do you think you will be able to eat today?" I do not want hyperglycemia to be the factor that extends hospital stay, so if the patient did not eat much the day before and was on clear liquids the previous night but now is ready to eat breakfast, I must start increasing the insulin, especially meal-related (prandial) insulin.

For patients on intravenous continuous nutrients, use of "coverage" insulin or a "sliding scale" alone is too late because the glucose level is already elevated. When managing patients on intravenous or (espe-

cially) oral nutrients, a preprandial dose of insulin along with sliding scale–based administration is effective when some basal insulin is already on board. For instance, if the patient normally takes 4 to 8 U of short-acting insulin before meals, and anticipates eating about half of his or her usual meal, administration of 2 U plus a correction bolus would be appropriate.

Compared with TPN, enteral feeding is associated with substantially lower insulin requirements. During enteral feeding, a compound called glucagon-like peptide-1 stimulates the pancreas to produce more insulin. Therefore, transitioning patients from TPN to enteral feeding may require reducing insulin doses by half if the pancreatic reserve is adequate.

When tube feeding is given at a continuous rate over 24 hours, frequent administration of intermediate- and short-acting insulin simulates "continuous" insulin administration. A regimen that works well consists of 70/30 insulin (70% NPH insulin and 30% regular insulin) given every 8 hours with "coverage" regular insulin given every 4 hours. Once during every 24-hour period, the total dose of coverage insulin is added into the total daily dose of 70/30 insulin (eg, if a patient is receiving 15 U of 70/30 insulin every 8 hours and requires a total of 15 U of regular insulin through the previous 24-hour period, the 70/30 insulin dose is increased to 20 U every 8 hours). This insulin regimen must be adjusted if the patient is going to receive nighttime feeding. If the patient receives continuous nutrients from 6:00 PM to 6:00 AM and will be fed during the day, we often will give NPH plus regular insulin at 6:00 PM and additional regular insulin at 10:00 PM and 2:00 AM, followed by a small amount of basal/bolus insulin during the day when he or she is eating. This is a circumstance in which we may use NPH insulin at night and insulin glargine during the day.

Complications

The presence of adrenergic symptoms, especially sweating, in diabetic patients does not always imply hypoglycemia. Such symptoms may also be a reflection of autonomic neuropathy or a sign of myocardial infarction or an infection. In patients with renal disease a drop in blood sugar levels may also be associated with acute renal failure.

In a patient with reasonably controlled blood glucose levels in the hospital, an unexpected increase in blood glucose values requires evaluation for a wound infection. Hyperglycemia may antedate fever. Glucose levels are a sensitive marker of counterregulatory hormones, which often are activated before patients become febrile.

Diabetic patients may be more susceptible to nerve palsies because they already are at risk for compressive neuropathies, which may be aggravated in the perioperative state.

Consider heel protectors if the patient's foot is insensate and at risk for ulceration, especially if there are preexisting calluses or foot deformities. Heel protectors are relatively inexpensive and reduce the risk for foot breakdown.

CASE 1: INSULIN MANAGEMENT AFTER CABG

A 65-year-old man with a 20-year history of diabetes has blood glucose values of 100 to 180 mg/dL on an insulin infusion of 2 U/hr intravenously in the ICU after coronary artery bypass graft (CABG) surgery. He had been treated preoperatively with a total daily insulin dose of 70 U (eg, 40 U of NPH insulin and 10 U of regular insulin before each meal). Which of the following insulin regimens should be used in transitioning to subcutaneous insulin?

A. Discontinue insulin drip and start regular insulin given on a sliding scale

B. Discontinue insulin drip and start a short-acting insulin analog (eg, insulin lispro or aspart) on a sliding scale

C. Discontinue insulin drip and start NPH insulin 5 U plus regular insulin on a sliding scale

D. Continue insulin drip for 2 hours and start NPH insulin 20 U plus regular insulin on a sliding scale

E. Continue insulin drip for 2 hours and start insulin glargine 20 U plus an insulin analog on a sliding scale

The best response is D, but E would also be acceptable. In general, when patients have been on NPH insulin, we tend to continue it. NPH insulin acts faster than insulin glargine, which has a slower onset and whose maximal effect may not be seen for a few days. Even though use of insulin glargine is increasing, data are more abundant on insulins that exert their effect hours instead of days after administration. The main message is to get adequate basal insulin on board.

Basal insulin needs are predicted by the patient's insulin needs prior to hospitalization and the insulin infusion rate. Starting the basal insulin at half the preoperative dose is generally safe. "Sliding scale" or coverage insulin alone is usually inadequate. The sliding scale is usually every 4 hours until the patient starts to eat, at which time he or she can be switched to premeal prandial insulin plus a correction dose for hyperglycemia.

Glucose level related to in-hospital mortality

Several retrospective analyses have shown an association between blood glucose level and hospital mortality in the post-CABG setting, with a flattening of the mor-

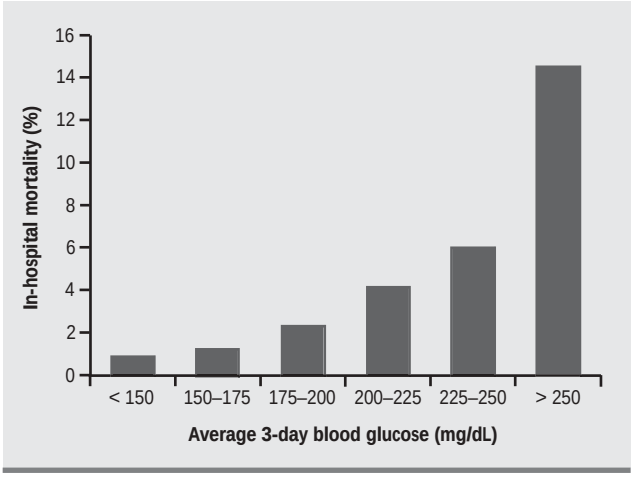

FIGURE 1. In-hospital mortality, by blood glucose level, among 3,554 patients with diabetes undergoing coronary artery bypass graft surgery from a retrospective analysis. The glucose-related increase in mortality ($P < .001$) was due overwhelmingly to increased cardiac-related mortality. Reprinted from reference 11, copyright 2003, with permission from American Association for Thoracic Surgery.

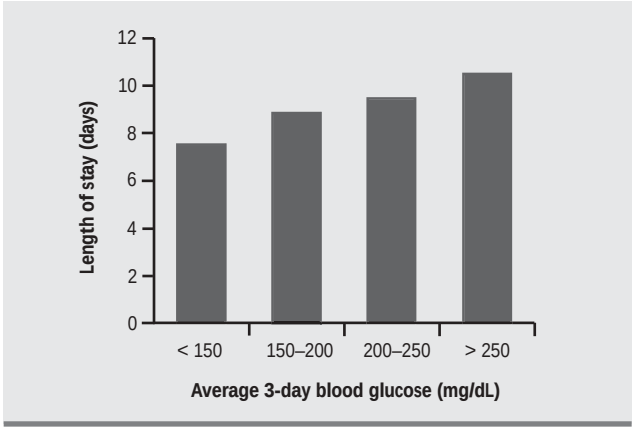

FIGURE 2. Length of hospital stay, by blood glucose level, among 2,105 patients with diabetes following coronary artery bypass graft surgery. Data from reference 12.

tality curve once the average 3-day blood glucose value falls below 150 mg/dL.[9–11] Figure 1 illustrates the findings from one of these studies.[11] The lowest threshold for blood glucose is not known, but the evidence is compelling in support of reducing levels to less than 200 mg/dL to reduce the risk of in-hospital mortality. A similar association has been observed between blood glucose and length of hospital stay (Figure 2).[12] It should be noted that these data were unadjusted for Acute Physiology and Chronic Health Evaluation (APACHE) scores, but they suggest a role for glucose control in reducing in-hospital mortality and length of stay.

Intensive insulin therapy for the critically ill

A large prospective study by Van den Berghe et al[13] showed that, among critically ill patients, intensive insulin therapy (to a target blood glucose of 110 mg/dL or lower) was superior to a conventional insulin infusion strategy (target blood glucose of 180 to 200 mg/dL) on several outcome measures. The intensive strategy was associated with a reduction in ICU mortality, from 8.0% to 4.6% (43% relative reduction), as well as substantial reductions in hospital mortality, ICU days, time on a ventilator, the incidence of renal failure, and the incidence of systemic infection (Table 1). Whether the insulin therapy itself or the blood glucose levels achieved were responsible for the risk reductions is uncertain, since insulin is an anabolic compound that may have effects other than lowering blood glucose.

CASE 2: GLUCOSE CONTROL AFTER POSTOPERATIVE STROKE

A 70-year-old white man has a postoperative stroke requiring continuous feeding via a feeding tube. His prehospital glucose regimen was a sulfonylurea plus metformin. His blood glucose values are greater than 180 mg/dL with a caloric intake of 20 kcal/hr, and his projected need is 70 kcal/hr. Which of the following regimens should be recommended?

A. Sulfonylurea and metformin (at preoperative doses)
B. Sulfonylurea, metformin, and a thiazolidinedione
C. Sulfonylurea, metformin, and regular insulin given on a sliding scale
D. NPH insulin 20 U every morning and 10 U every evening with regular insulin four times daily
E. 70/30 insulin 10 U every 8 hours plus regular insulin on a sliding scale every 4 hours

My philosophy is that perioperative glucose management in the hospital consists of insulin administration. Insulin is safe for patients of any age; can be given to patients with heart, liver, or kidney failure; has a rapid onset and clearance; has few drug interactions; and has been used for more than 8 decades. Many diabetic patients will require insulin later in their disease course, and the perioperative setting provides an excellent opportunity for teaching them how to administer it.

Regular insulin at low doses has a peak effect at 3 to 4 hours and a duration of 6 to 8 hours, whereas NPH insulin has a peak effect at 6 to 10 hours and a duration of 18 to 24 hours. The pharmacokinetic principle behind 70/30 insulin is that the overlapping half-lives of an intermediate-acting insulin and regular insulin (which has a more rapid onset) will produce near steady-state plasma insulin concentrations.

The regimen I would recommend, consistent with Cleveland Clinic practice, is to start with 70/30 insulin and then add regular insulin given subcutaneously on a sliding scale every 4 hours. As noted above, if the sliding scale coverage during the previous 24 hours totals 15 U, then 5 U should be added to each of the three doses of 70/30 insulin. In addition, as the tube feeding rate increases, a corresponding increase in the 70/30 dose should be implemented at the same time. For example,

TABLE 1
Outcomes with conventional vs intensive insulin therapy in critically ill patients

	Conventional therapy (n = 783)	Intensive therapy (n = 765)	Relative risk reduction	*P*
Death in intensive care unit	8.0%	4.6%	43%	< .04*
Death in hospital	10.9%	7.2%	34%	.01
> 14 days in intensive care unit	15.7%	11.4%	28%	.01
Ventilator required > 14 days	11.9%	7.5%	37%	.003
Renal failure	8.2%	4.8%	41%	.007
Septicemia in intensive care unit	7.8%	4.2%	46%	.003

* *P* value adjusted for repeated interim analyses.
Adapted from reference 13.

if a patient needs 10 U every 8 hours for a tube feeding rate of 30 mL/hr, one can estimate that at least twice this dose will be needed for a rate of 60 mL/hr, and this change can be incorporated into insulin orders.

With this regimen and a continuous nutrient intake, the blood glucose can be stabilized within 24 hours and maintained safely in the range of 100 to 120 mg/dL—and possibly lower. The risk of hypoglycemia with such a regimen is low in patients receiving continuous nutrients.

Other options include frequent doses of NPH or 50/50 insulin, or insulin glargine twice daily, although the onset of action of insulin glargine would be slower than the alternatives mentioned.

What about oral antidiabetic agents?

There is little role for oral agents in the immediate postoperative phase. Oral agents can be started postoperatively when the patient starts eating again; at this point in the postoperative period there is little need to worry about the ischemic preconditioning associated with some of the first- and second-generation sulfonylureas. Metformin can be restarted if the renal function is stable and nausea is not a concern. Carbohydrase inhibitors (eg, acarbose, miglitol) have a rapid onset, whereas thiazolidinediones (eg, pioglitzone, rosiglitazone) have a slower onset. Short-acting insulin secretagogues (eg, meglitinide, nateglinide) can also be considered.

SUMMARY

Patients with diabetes mellitus are at higher risk for complications from surgery than their nondiabetic counterparts. Evidence-based guidance on the perioperative management of diabetic patients is still very limited. Management is best guided by careful preoperative and postoperative consideration of diet, antidiabetic medication regimens, and the likelihood of specific complications of diabetes. Good postoperative glucose control reduces the risk of in-hospital death and shortens length of stay. Insulin is the mainstay of perioperative glucose management, and intensive insulin therapy (to a target blood glucose of 110 mg/dL or lower) improves a range of clinical outcomes in critically ill patients relative to less aggressive insulin strategies. There is little role for oral antidiabetic medications in the early postoperative phase.

REFERENCES

1. Clement S, Braithwaite SS, Magee MF, et al; American Diabetes Association Diabetes in Hospitals Writing Committee. Management of diabetes and hyperglycemia in hospitals. Diabetes Care 2004; 27:553–591.
2. Garcia MJ, McNamara PM, Gordon T, Kannell WB. Morbidity and mortality in diabetics in the Framingham population. Sixteen-year follow-up study. Diabetes 1974; 23:105–111.
3. Abbott RD, Donahue RP, Kannel WB, Wilson PW. The impact of diabetes on survival following myocardial infarction in men vs women. The Framingham Study. JAMA 1988; 260:3456–3460.
4. Donahue RP, Goldberg RJ, Chen Z, Gore JM, Alpert JS. The influence of sex and diabetes mellitus on survival following acute myocardial infarction: a community-wide perspective. J Clin Epidemiol 1993; 46:245–252.
5. Stamler J, Vaccaro I, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-year cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. Diabetes Care 1993; 16:434–444.
6. Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet 2004; 364:937–952.
7. American Diabetes Association. Standards of medical care in diabetes. Diabetes Care 2005; 28(Suppl 1):S4–S36.
8. Juul AB. Randomized, blinded trial on perioperative metoprolol versus placebo for diabetic patients undergoing noncardiac surgery [abstract]. Presented at: American Heart Association Scientific Sessions; November 7–10, 2004; New Orleans, LA.
9. Zerr KJ, Furnary AP, Grunkemeier GL, Bookin S, Kanhere V, Starr A. Glucose control lowers the risk of wound infection in diabetics after open heart operations. Ann Thorac Surg 1997; 63:356–361.
10. Furnary AP, Zerr KJ, Grunkemeier GL, Starr A. Continuous intravenous insulin infusion reduces the incidence of deep sternal wound infection in diabetic patients after cardiac surgical procedures. Ann Thorac Surg 1999; 67:352–360.
11. Furnary AP, Gao G, Grunkemeier GL , et al. Continuous insulin infusion reduces mortality in patients with diabetes undergoing coronary artery bypass grafting. J Thorac Cardiovasc Surg 2003; 125:1007–1021.
12. Furnary AP, Chaugle H, Zerr KJ, Grunkemeier GL. Postoperative hyperglycemia prolongs length of stay in diabetic CABG patients [abstract]. Circulation 2000; 102(Suppl II):556. Abstract 2703.
13. Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. N Engl J Med 2001; 345:1359–1367.