Role of Insulin in Management of Surgical Patients With Diabetes Mellitus

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Because surgery is a likely event during the lifetime of patients with diabetes, health-care team members need to be aware of the metabolic problems that may occur during the perioperative period. Surgery, especially in the presence of general anesthesia, will produce a diabetogenic response. This is generally due to an elevation of counterregulatory hormones, although endogenous insulin is also suppressed. The excessive lipolysis and ketogenesis that can occur during surgery can have particularly deleterious effects for patients with diabetes. Thus, sufficient insulin must be provided during this period to suppress these catabolic processes. The major controversy regarding surgery and diabetes concerns the route of insulin administration. This article reviews the various treatment options for patients with insulin-dependent and non-insulin-dependent diabetes mellitus, with particular emphasis on the role of insulin. Special situations, e.g., outpatient surgery, coronary artery bypass, and emergency surgery, are also discussed. *Diabetes Care* 13:980–91, 1990

During the 1960s, it was estimated that diabetic patients had a 50% chance of undergoing surgery at some point during their lifetime (1). Due to advances in medical and surgical therapies, it is likely that diabetic individuals have an even greater chance of requiring surgery today. The types of surgery performed are influenced by the complications related to diabetes, which include kidney transplantation, penile prothesis implantation, and ulcer debridement. Diabetic patients are also subject to the same operations required by nondiabetic patients. For example, in 1980, 11.3% of operations performed on diabetic patients in the United States were on the cardiovascular system, compared to 4.3% in nondiabetic people, and ophthalmologic procedures comprised 5.5% compared to 3.3% (2).

There are several reasons to attempt to normalize plasma glucose levels in the perioperative period. In the case of insulin-dependent diabetes mellitus (IDDM), inadequate attention to blood glucose levels can result in ketosis and acidemia, whereas all patients with glucose intolerance are susceptible to electrolyte abnormalities and volume depletion from osmotic diuresis. There are also data indicating impaired wound strength and wound healing with plasma glucose levels of >11.1 mM (3–6). Hyperglycemia interferes with the leukocyte functions of chemotaxis, opsonization, and phagocytosis (7). Finally, both animal and human studies suggest that hyperglycemia exacerbates ischemic brain damage (8–10). Still, despite the technical ability to nearly normalize glycemia, prospective data are not available comparing surgical outcomes after improved blood glucose control during the perioperative period.

Over the past few years, there have been several excellent reviews concerning the management of the diabetic patient during surgery (11–14). In this article, the metabolic effects of anesthesia and surgery are discussed, with special emphasis on the role of insulin. In addition, treatment options for diabetes management during the perioperative period are reviewed.

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HORMONAL CONTROL OF GLUCOSE HOMEOSTASIS

Hormonal regulation of glucose homeostasis may be broadly categorized into hormones having chiefly catabolic effects and insulin, which may be considered the primary anabolic hormone. The former group, which includes epinephrine, glucagon, cortisol, and growth hormone, is considered counterregulatory hormones. However, as shown in Table 1, this simplistic classification is not completely valid for the counterregulatory hormones, i.e., fat and protein metabolism. Therefore, the physiological roles of these hormones are characterized separately. Subsequently, the role of each hormone during the perioperative period is discussed.

Insulin. Insulin suppresses endogenous glucose production (both glycogenolysis and gluconeogenesis) and stimulates glucose utilization. Therefore, unless there are other intervening factors, increases in insulin secretion would lower the plasma glucose level. Inhibition of gluconeogenesis requires greater amounts of insulin than suppression of glycogenolysis. For example, in dogs, a mean immunoreactive insulin level of 438 pM results in complete suppression of glycogenolysis but persistence of gluconeogenesis (15). Although plasma glucose level is the major regulator of insulin secretion, absorbed amino acids after a mixed meal will further amplify the insulin response (16).

In protein metabolism, there are four mechanisms by which insulin may increase body protein stores: *1*) increased tissue uptake of amino acids, *2*) increased protein synthesis, *3*) decreased proteolysis, and *4*) decreased oxidation of amino acids.

Insulin stimulates fatty acid synthesis in the liver and accelerates the removal of circulating triglycerides by inducing the synthesis of lipoprotein lipase in adipose tissue. In addition, insulin effectively inhibits hormone-sensitive lipase, which catalyzes the hydrolysis of stored triglycerides. Indeed, the antilipolytic effect of insulin is considered its most sensitive action. Nurjham et al. (17), with a euglycemic clamp, showed an ED_{50} of 90 pM for antilipolytic activity versus 180 pM for inhibition of hepatic glucose production.

Insulin also has a profound suppressive effect on blood ketone levels. Insulin deficiency leads to ketoacidemia due to *1*) unrestrained mobilization of free fatty acid (FFA) from adipose tissue, *2*) accumulation of hepatic acetyl-CoA due to excessive FFA oxidation, and *3*) a reduction in ketone utilization by peripheral tissues. The antiketogenic action of insulin is related to both its inhibition of hepatic carnitine levels and its stimulation of intrahepatic lipogenesis, thereby increasing malonyl-CoA availability (18). Carnitine is the fatty acyl-CoA molecule required for mitochondrial membrane penetration. The enzyme carnitine acyltransferase I(CAT I) catalyzes the formation of the fatty acyl-carnitine derivative, and malonyl-CoA directly inhibits CAT I. Thus, the reduced carnitine concentrations and increased malonyl-CoA levels are responsible in directing fatty acyl-CoA into microsomes for esterification to triglycerides, rather than ketone production.

Epinephrine. Epinephrine stimulates glucose production and limits glucose utilization; each of these are accomplished by direct and indirect actions (19). The indirect mechanisms are largely mediated through α_2-inhibition of insulin secretion and β-stimulation of glucagon secretion (16,19). The direct actions of epinephrine occur via β-adrenergic mechanisms; glucose utilization is inhibited, whereas glucose production is stimulated (20). Both glycogenolysis and gluconeogenesis are stimulated by epinephrine, and plasma glucose increases within minutes; however, this effect is transient (20; Table 1). Nevertheless, because the limitation of glucose utilization is sustained, the plasma glucose level remains elevated (19).

Other metabolic effects of epinephrine include *1*) stimulation of lipolysis and ketogenesis (21), *2*) reduction of net proteolysis with decreased circulating amino acid (except alanine) levels (22,23), and *3*) increased thermogenesis (24). These actions also account for accumulation of the gluconeogenic substrates (lactate, alanine, and glycerol), which contribute to gluconeogenesis.

Glucagon. Like insulin, plasma glucose is the major regulator of glucagon secretion. As the glucose level rises, glucagon secretion is suppressed; a decline in glucose levels will stimulate glucagon secretion (16). Except for amino acids (which stimulate both glucagon and insulin secretion), glucagon secretion is reciprocal to insulin secretion. Thus, although increases in plasma glucose levels will suppress glucagon secretion, hypoglycemia, fasting, and stress will stimulate it.

Increments in plasma glucagon level produce a rise in plasma glucose by stimulating hepatic glycogenolysis and gluconeogenesis. These actions last <45 min (25). Hepatic glucose metabolism is influenced by changes in glucagon levels compared with absolute levels (25). Other important actions of glucagon include increasing hepatic ketogenesis and decreasing hepatic glycogen formation, glycolysis, and triglyceride synthesis (26). Although other catabolic hormones may play a role in the induction of ketogenesis, it is believed that glucagon is the primary signal of regulating this process (26).

Cortisol. Cortisol impairs carbohydrate tolerance by decreasing glucose utilization. Short-term cortisol excess reduces glucose utilization at physiological insulin levels. Chronic cortisol excess (e.g., Cushing's syndrome) is associated with an impaired glucose utilization at both physiological and supraphysiological insulin levels (27). This effect is mediated, at least in part, by a decrease in binding of insulin to its receptor (28).

Cortisol can also increase gluconeogenesis directly by gluconeogenic enzyme induction and indirectly by increasing substrate availability (28). Both proteolysis and lipolysis are stimulated by cortisol (29,30). In addition, cortisol exhibits permissive effects of glucagon and ep-

TABLE 1
Metabolic effects of anabolic and catabolic hormones

	Anabolic effects			Catabolic effects			
	Glycogenesis	Lipogenesis	Protein synthesis	Glycogenolysis	Gluconeogenesis	Lipolysis	Proteolysis
Insulin	+	+	+	−	−	−	−
Epinephrine	−	0	0	+	+	+	−
Glucagon	−	0	0	+	+	?*	+
Cortisol	±	±	−	−	+	+	+†
Growth hormone	0	0	+	−	+	+	+†

+, Stimulatory effect; −, inhibitory effect; 0, no effect; ±, stimulatory in presence of insulin, inhibitory in absence of insulin.
*Effects increased with nonphysiological levels.
†Effects important in absence of insulin.

inephrine on gluconeogenesis (31). Cortisol also has the anabolic action of increasing the activity of glycogen synthase (32). In insulin-deficient states, however, cortisol has potent ketogenic effects (33).

Growth hormone. Transient acute insulinlike effects of growth hormone have been described, affecting protein, lipid, and carbohydrate metabolism (34). However, tissues become refractory to these effects over the course of a few hours. Chronic growth hormone excess impairs insulin action, suppresses glucose utilization, and stimulates glucose production (35). Growth hormone also has important anabolic properties regarding protein synthesis (36).

Elevated growth hormone levels after 1–2 h result in accelerated lipolysis and ketogenesis, although the latter appears to be secondary to the increase in fatty acid delivery to the liver compared with a direct effect (34). This lipolytic action of growth hormone is overcome by insulin; furthermore, growth hormone does not diminish the antilipolytic efficacy of insulin (37).

METABOLIC EFFECTS OF SURGERY

Surgery, especially in the presence of general anesthesia, will produce a diabetogenic response (Fig. 1). Hyperglycemia during surgery or postoperatively can occur in nondiabetic patients (38–45). The magnitude of the plasma glucose rise is related in part to glucose infusion rates (44). The hormonal etiology of this form of hyperglycemia is (relative) deficient insulin and C-peptide secretion, in addition to insulin resistance (38–40,42–49). The precise cause of this insulin resistance is unclear, but it is thought to be due to elevated counterregulatory hormone levels. Catecholamine increases are the rule during general anesthesia, although this is probably dependent on the anesthetic agent (50,51). Epinephrine stimulates muscle glycogenolysis which, besides providing fuel for muscle, provides lactate for hepatic gluconeogenesis. ACTH and cortisol levels are also elevated in the preoperative period, although this is also dependent on the anesthetic agent (42,44,45,47,49,52–58). Similarly, growth hormone has been shown to be increased in most but not all studies (44,45,47,59,60). Glucagon levels have been the most variable of the counterregulatory hormone measurements during the perioperative period. Decreases, increases, and stable glucagon levels have been reported (45,57,61,62). One study showed stable intraoperative glucagon levels but increased postoperative levels (47).

Taken together, the above processes can be expected to result in excessive glycogenolysis, gluconeogenesis, lipolysis, and proteolysis during the perioperative period. However, in the nondiabetic subject, fat metabolism is different than expected. Glycerol and FFA levels are lower in surgical subjects compared with nonoperated subjects fasted for a similar period (62). Blood ketone body levels are also decreased, due in part to the lower substrate supply to the liver and to a specific intrahepatic deficit (63). This relative impairment of lipolysis is probably due to the increased insulin levels. The negative nitrogen balance that occurs postoperatively can be primarily attributed to cortisol and proteolysis-inducing factor (PIF; 64). PIF exerts its effect through increased synthesis of prostaglandin 2 and may be an active cleavage product of interleukin 1, although this remains to be clarified (65,66).

It appears that central neural blockade has only a limited impact on metabolic function. No significant changes have been noted in blood glucose, lactate, alanine, FFA, glycerol, and ketones during 20–30 min of epidural anesthesia (67). Data also suggest that epidural anesthesia has no important effect on plasma cortisol and growth hormone levels (68). However, plasma epinephrine and norepinephrine levels decrease proportionally to the level of sensory analgesia achieved during spinal anesthesia with tetracaine (69). The insulin response to hyperglycemia appears to be inhibited by a high-thoracic (T2-T6 dermatome) blockage, whereas a low-thoracic blockage has no effect on insulin secretion (70). Earlier studies are supported by a report that showed a marked amelioration of the metabolic and endocrine response to surgery in patients given a splanchnic nerve block (71).

The effects of high levels of the counterregulatory hormones, although not usually deleterious to the nondi-

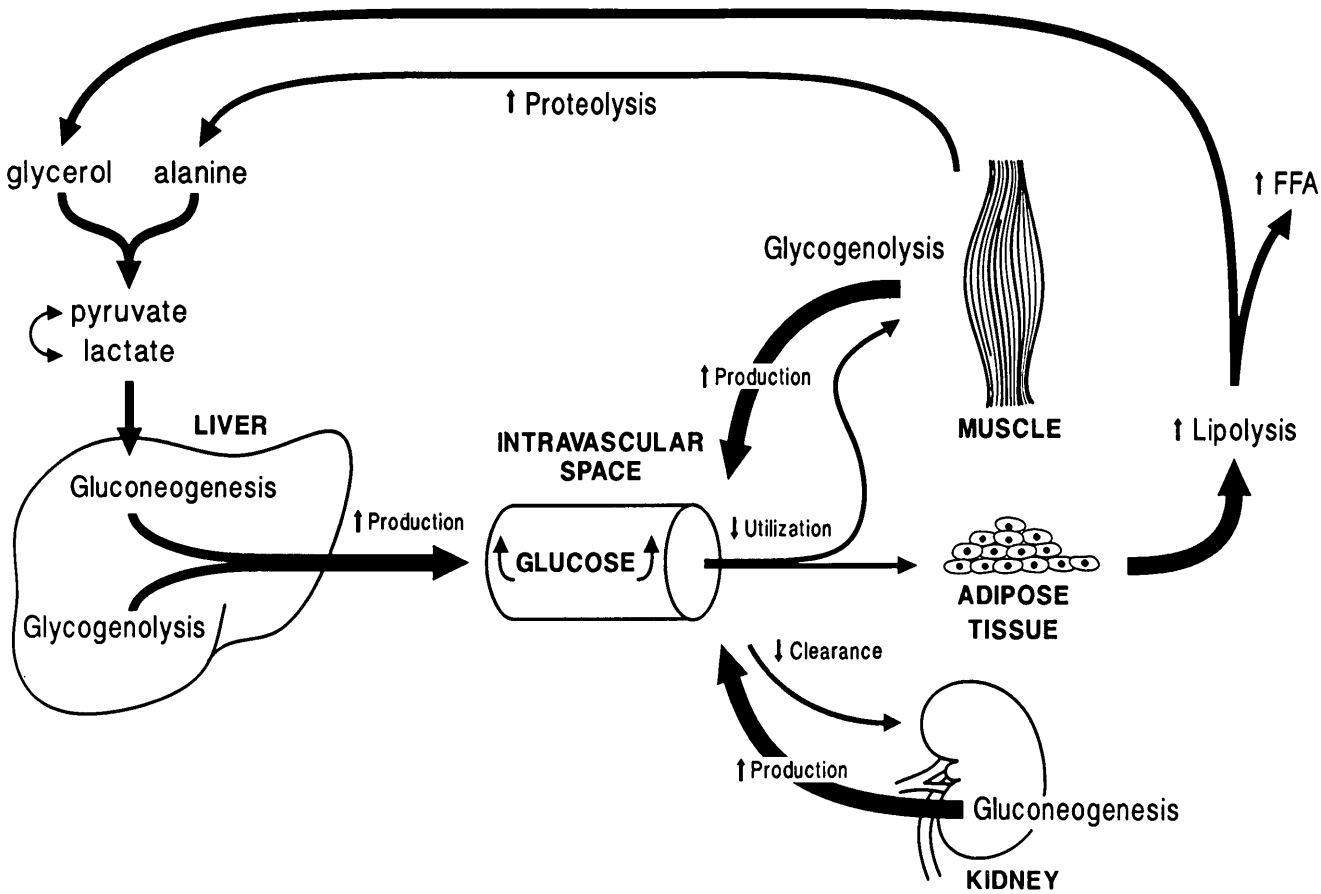

FIG. 1. Factors resulting in hyperglycemia during surgery. Increased glucose production is due to hepatic and muscle glycogenolysis and hepatic and renal gluconeogenesis. Renal clearance of glucose from circulation may be decreased during volume depletion. Relative insulin deficiency inhibits glucose utilization.

abetic patient, can contribute to major metabolic derangements in patients with IDDM. A different effect is encountered in the patient with non-insulin-dependent diabetes mellitus (NIDDM), who may be prone to excessive hyperglycemia, dehydration, and hyperosmolarity secondary to decreased insulin sensitivity. Providing a stable metabolic milieu in the face of this exaggerated counterregulatory hormone response to ensure an optimal surgical outcome is the task of the diabetology/surgery/anesthesiology team members. It is important to appreciate that massive plasma glucose elevations are not necessary for metabolic decompensation. Indeed, it is possible for a patient with IDDM to develop ketoacidosis with a plasma glucose level only moderately elevated. One study showed that 17% of all diagnoses of diabetic ketoacidosis (DKA) were in patients with plasma glucose levels <16.7 mM, but values <5.6 mM have been encountered. This phenomenon is called euglycemic DKA (72,73). Although less marked in the patient with NIDDM, changes in protein and fat metabolism might be expected due to the inability of these patients to increase insulin secretion in response to surgery-induced hyperglycemia. In both groups of patients, careful management coupled with frequent monitoring of plasma glucose, electrolytes, and urinary ketones can prevent serious pertubations.

ELECTIVE SURGERY IN PATIENTS WITH IDDM

Preoperative evaluation. Due to the potentially deleterious metabolic effects of surgery, preoperative evaluation and treatment to correct hyperglycemia and electrolyte abnormalities is imperative. Some authors recommend admitting patients with IDDM 48–72 h before surgery, with the intent to improve metabolic control and assess cardiovascular status (11,74), but the high costs involved with this strategy have made these longer admissions prohibitive. Indeed, many diabetic patients are now admitted on the morning of surgery. With the widespread use of self-monitoring of blood glucose, it should be possible to correct serious hyperglycemia before admission.

Preoperative assessment should include basic cardiovascular and renal testing (ECG, urinary dipstick for proteinuria, serum creatinine measurement). In one study, the most common cause of perioperative mortality was coronary artery disease (29%; 75). One recent study

suggested that diabetic patients should also be screened for autonomic neuropathy before surgery because these patients are at high risk for developing perioperative hypotension (76).

The regimen for achieving optimal preoperative glycemic control is arbitrary. There are several acceptable insulin regimens (77). Patients who use ultralente insulin at home may be changed to an intermediate-acting insulin 3 days before surgery (11). Some would consider this inconvenient, and there have been no studies that examined problems with long-acting insulin perioperatively.

Intraoperative management. The major controversy in insulin management during surgery is the route of insulin administration (14). Some authors advocate subcutaneous insulin administration (74), but more are now recommending intravenous insulin infusion (IVII) therapy (11,13,78,79). It would be expected that erratic insulin absorption, which normally occurs with subcutaneous insulin administration, would become even more pronounced with the fluid shifts and hemodynamic changes that occur in the perioperative period (80,81).

Taitelman et al. (82) were the first to report the use of an IVII in diabetic patients during surgery. These authors and others showed that fixed-rate IVII of 1 U/h offered no advantage over subcutaneous insulin administration (47). Thomas et al. (83) later reported on the efficacy and safety of a glucose/insulin/potassium (GIK) infusion. Several authors have advocated the use of intermittent intravenous boluses of insulin (84,85). In the study by Walts et al. (84), insulin was not given more than once every 2 h to one group of patients. This group had no rise in their plasma glucose levels after 4 h of surgery. However, this study included patients with IDDM and NIDDM. Because the half-life of intravenous insulin is between 4 and 5 min, with a biological half-life of <20 min (except in patients with antibodies to insulin; 86), few would recommend intermittent intravenous boluses of insulin in ketosis-prone diabetic patients.

The variable-rate IVII used by Watts et al. (87) was reported to be safe and efficacious. They showed a wide range of insulin requirements (0.5–5.0 U/h) during insulin infusion based on an algorithm-dependent program in a group of patients with IDDM and NIDDM (protocol patients). Within 8 h, the mean blood glucose level was within the target range of 6.7–10.0 mM, and it remained stable for the remainder of the study.

The control group who received either a conventional subcutaneous sliding scale or fixed-rate IVII had a final glucose level ranging from 1.7 to 17.0 mM at 12–24 h after surgery. The danger of the conventional therapy is obvious. Control patients also had higher mean plasma glucose levels compared with protocol patients (11.6 ± 1.1 vs. 7.6 ± 0.8 mM, $P < 0.05$). The decision to use a GIK infusion or variable-rate IVII is a matter of preference. We prefer the latter due to increased flexibility of altering insulin delivery rates. With the GIK infusion, 16 U of regular insulin and 10 meq potassium chloride are added to 500 ml of 10% dextrose (11). For blood glucose levels >10 mM, the entire bag needs to be changed with a total of 20 U regular insulin/500 ml 10% dextrose. Similarly, for every blood glucose level measured >10 mM, additional increments (4 U) of insulin need to be added to a new bag. Blood glucose levels between 5 and 10 mM require no change, whereas blood glucose levels <5 mM require decrements of insulin in 4-U increments. Obviously, if blood glucose levels are catastrophically high or low, more significant changes will be needed.

Despite the fact that IVII has been recommended by investigators for the last decade, actual intraoperative management practices have not totally reflected these changes. It was recently shown in a larger American teaching hospital study (88) that perioperative management practices in a group of patients with IDDM were similar to those used in the 1962 article by Galloway and Shuman (75). Of the 76 patients who used NPH insulin at home, 61 (80%) were given half of their morning dose of NPH insulin before surgery (88; Fig. 2). Regular insulin was administered preoperatively to 23 of 85 patients (27%) who used short-acting insulin at home. Intraoperatively, 52% of patients received no insulin, whereas the remaining 48% received it primarily by intermittent intravenous boluses (Fig. 3). Only 5% of the patient population received insulin from IVII.

Even more discouraging from this study was the infrequency of blood glucose and electrolyte monitoring. Thirty-five percent of patients did not have even one blood glucose measurement during surgery. Seven of 11 patients with postoperative hypoglycemia (blood glucose level <3.3 mM) did not have intraoperative blood glucose measured, and only 20% of the patients had postoperative electrolyte determinations. Although there were no deaths in this study, there was one episode of postoperative DKA. Furthermore, there was a significant negative correlation between changes in postoperative electrolytes (from admission) and glucose levels (Fig. 4).

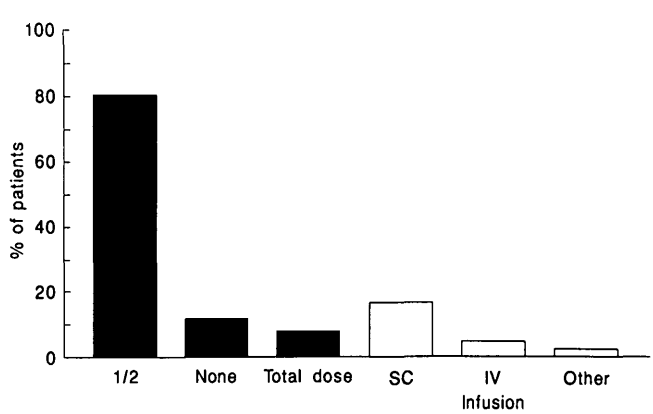

FIG. 2. Preoperative insulin administration in surgical patients with insulin-dependent diabetes mellitus at American teaching hospital. *Solid bars*, 76 patients who use intermediate-acting insulin at home; *open bars*, 85 patients receiving short-acting insulin at home (88). SC, subcutaneous; IV, intravenous.

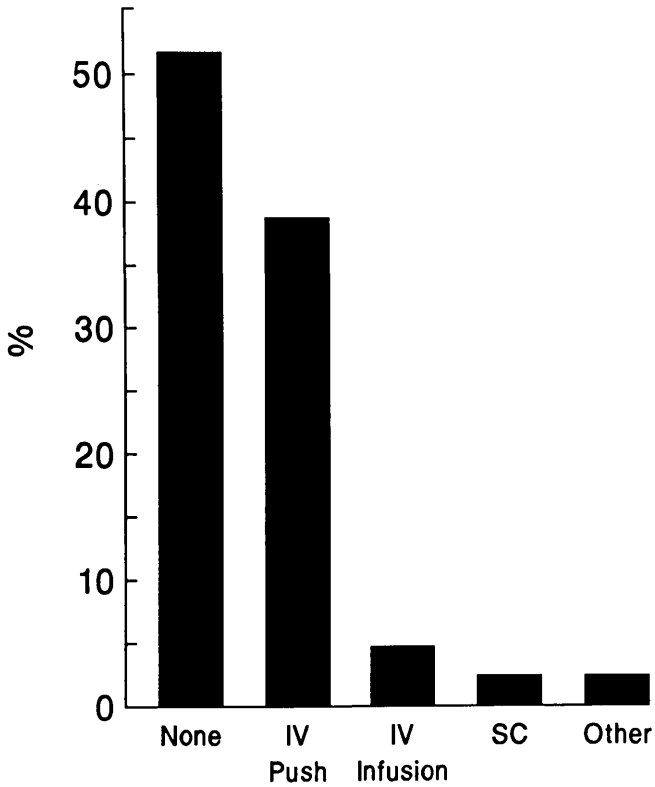

FIG. 3. Intraoperative regular insulin administration in 85 patients with insulin-dependent diabetes mellitus at American teaching hospital (88). SC, subcutaneous; IV, intravenous.

It can only be speculated that inadequate subcutaneous insulin administration in the setting of elevated counterregulatory hormone levels resulted in ketoacid accumulation. Obviously, prospective studies examining the pharmacokinetics and metabolic effects of perioperative subcutaneous and intermittent intravenous boluses of insulin are needed.

Although perioperative glycemic goals are arbitrary (6.6–10 vs. 10–14 mM; 74,87), it is imperative that insulin and glucose infusions are matched. The current recommendation calls for 0.25–0.35 U insulin/g glucose, although insulin-resistant states (obesity, sepsis, glucocorticoid excess) will mandate larger ratios (14,89). Patients undergoing cardiopulmonary bypass are perhaps the most insulin resistant (90). Hypothermia, large volumes of glucose-containing fluids, and use of adrenergic agents all have deleterious metabolic effects in the diabetic patient (19,45,91).

Glucose. The average nondiabetic adult needs a minimum of 100–125 g (400–500 cal) exogenous glucose/day for protein sparing and ketosis prevention (92,93). Although this quantity of glucose was considered adequate for a 50% reduction in protein catabolism during starvation (93), another study found that postoperative patients receiving 100 g glucose/day had only a 23% decrease in urinary nitrogen (94). Wolfe and Peters (95) showed that in fasting healthy volunteers, glucose infused at a rate of 1 mg · kg^{-1} · min^{-1} (4.2 g/h for a 70-kg man) had no effect on the rate of release of glycerol or FFA. However, at 4 mg · kg^{-1} · min^{-1} (16.8 g/h for a 70-kg man), the rates of both release of glycerol and FFA were suppressed. This type of kinetic study has not been performed during surgery. The prevention of ketone body and FFA accumulation in all surgical patients is theoretically important because elevated levels of circulating FFA have been shown to increase myocardial oxygen consumption and, in some instances, the risk of arrhythmias (96,97).

Patients should be given sufficient glucose to prevent hypoglycemia and to provide basal energy requirements during surgery. Some authors recommend 10 g glucose/h (2.4 mg · kg^{-1} · min^{-1}), although others suggest 5 g/h (1.2 mg · kg^{-1} · min^{-1}; 1,11,78,79,87). Additional studies are needed to determine how much glucose is required to prevent unnecessary fat and protein catabolism.

Fluids. In general, a standard solution of 5% dextrose in 0.45% saline is infused at a rate that will provide adequate calories and replacement fluids. Any additional fluids should be nonglucose containing. However, if fluids need to be restricted, glucose can be given as 20 or 50% solutions at slower rates. When 20 or 50% solutions are used, infusion via a central venous catheter is recommended because the concentrated fluids increase the risk of peripheral venous thrombosis.

Although lactated Ringer's solution is widely used during surgery, lactate is a gluconeogenic precursor that is rapidly metabolized, particularly in a starved or catabolic state (98). Thomas and Alberti (99) showed that patients with NIDDM not receiving intravenous fluids during surgery had a mean plasma glucose rise of 2.2 mM, whereas those receiving lactated Ringer's solution (29–44 mmol) had a mean plasma glucose increase of

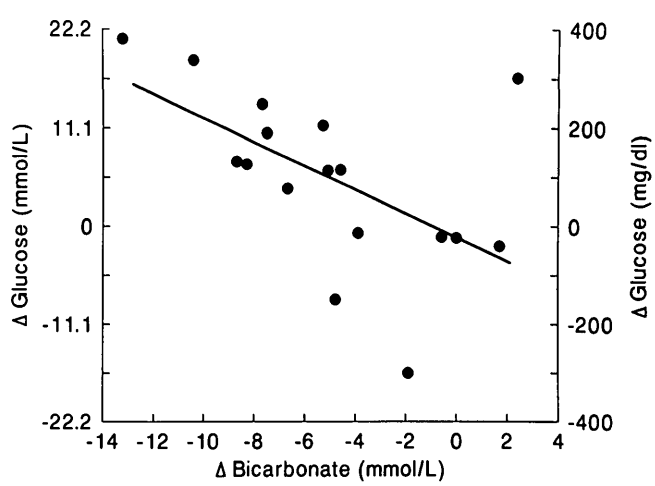

FIG. 4. Changes in blood glucose and bicarbonate levels (admission to postoperative) in 17 patients with insulin-dependent diabetes mellitus undergoing surgery ($R = -0.53$, $P < 0.05$; 88).

7.5 mM. Higher insulin dosages may be required for diabetic patients receiving lactated Ringer's solution during the perioperative period. In a recent study, however, the infusion of lactate at the rate of 25 μmol · kg^{-1} · min^{-1} over 3 h (~300 mmol) in nondiabetic subjects did not alter plasma glucose production (100). Additional study regarding the effects of lactated Ringer's solution in the diabetic population undergoing surgery is needed.

Postoperative management. Although there have been many recommendations for the postoperative management of patients with diabetes, no controlled studies have been performed comparing postoperative regimens when the preoperative and intraoperative regimens were similar. There appears to be no advantage in the use of a sliding-scale subcutaneous insulin regimen after surgery. Although this is a simple method for handling diabetic patients postoperatively, traditional sliding-scale regimens are based on retrospective hyperglycemia and tend to induce major swings in plasma glucose levels. Besides the erratic insulin absorption that can be expected during this time, the sliding scale is based only on guess work.

With a variable-rate IVII or GIK infusion, postoperative management is simple and flexible. Capillary glucose can be monitored at the bedside every 1–2 h, and appropriate adjustments can easily be made to achieve target blood glucose values. Some find it easier to stop the insulin infusion when food is first eaten, but we prefer to continue the insulin infusion through the first meal in the event of postoperative vomiting (14). The usual insulin regimen may be reinstituted when the IVII is stopped.

Outpatient surgery. Just as trends in diabetes care have changed, operations that in the past would have only been considered as inpatient procedures are now routinely performed on an outpatient basis. Although the procedures may be considered minor by patients and their surgeons, general anesthesia is still required in most cases (101). Because major changes in counterregulatory hormones can occur during minor procedures under general anesthesia, it is more logical to classify patients as inpatient versus outpatient. Indeed, the metabolic pertubations are similar in each surgical population.

There are few studies examining the treatment options for outpatient operations in patients with IDDM. Christiansen et al. (102) compared two groups of IDDM patients having minor surgery under general anesthesia. One group received an insulin-glucose infusion, and the other received conventional subcutaneous insulin therapy. The former group had significantly better blood glucose control, although there were no differences beween the two groups in lactate, β-hydroxybutyrate, and glycerol levels (FFA was not measured). Unfortunately, C-peptide measurements were not made. Because the mean age of both groups was 52 yr (with patients >70 yr of age in both groups), it is likely that some of the subjects were actually patients with NIDDM. This could, at least in part, explain why there were no differences in the measured metabolites. Nevertheless, this study suggests that insulin-deficient patients are optimally managed with an IVII during surgery.

There will be many situations where it is acceptable to use a subcutaneous regimen during brief outpatient surgical procedures. The decision not to begin an insulin infusion will depend on *1*) the outpatient's current metabolic status (e.g., individual with marked hyperglycemia and/or acidemia should be placed on an insulin infusion), *2*) preoperative insulin regimen (e.g., it would be easier to continue with subcutaneous insulin for patients who use beef or pork ultralente insulin), *3*) type of diet the outpatient will be allowed to eat after the operation, and *4*) the physician's ability to handle a metabolic crisis related to protracted postoperative nausea and vomiting, a common complication after outpatient anesthesia (103). It was recently reported that 18% of unanticipated hospital admissions after ambulatory surgery on a general patient population were due to intractable vomiting (104). Furthermore, because nausea and vomiting can be early harbingers to DKA, close blood glucose, electrolyte, and urinary ketone monitoring is necessary for any diabetic patient with postoperative emesis.

If the patient is to receive subcutaneous insulin for an outpatient operation, there are several strategies that can be used to achieve metabolic stability. If the patient normally takes NPH and regular insulin before breakfast and supper, 50–66% the usual dose of each type of insulin can be given in the morning unless there is evidence for fasting hypoglycemia or near hypoglycemia (blood glucose <4.4 mM). In the latter case, the regular insulin dose can be held until the capillary glucose level is >6.7 mM. The lower dosage of NPH insulin will reduce the risk of afternoon hypoglycemia if surgery is delayed or the patient develops postoperative emetic sequelae. Because supplemental regular insulin can be given later in the day, the full dose of NPH insulin is not necessary. The patient should be given a glucose infusion (5 g/h), and capillary glucose levels should be checked hourly.

If oral intake is tolerated immediately after the procedure, the remainder of the morning regular insulin should be given 20–30 min before resuming a regular diet. However, additional regular insulin may be needed if the capillary glucose level is >11.1 mM. This regimen depends on a degree of guesswork and may be associated with misjudgment.

The patient who takes animal-species ultralente insulin should be given the usual dose of this type of insulin. Regular insulin is only necessary for capillary glucose levels of >11.1 mM. Decreasing the ultralente insulin dose on the morning of surgery will have no effect on plasma glucose levels during the procedure, and changing to a different type of insulin several days before the procedure is unnecessarily complicated for patients undergoing brief ambulatory surgical procedures.

ELECTIVE SURGERY IN PATIENTS WITH NIDDM

Ambulatory surgery. Most patients undergoing surgery have NIDDM, although there has been less attention paid to the management of diabetes in this population. Due to the high prevalence of macrovascular disease in these patients, many in this group will have angiographic studies, angioplasties, ulcer debridements, and abscess drainage procedures that often can be performed on an outpatient basis (105). In addition, this population will frequently present for cataract extraction (106).

Most agree that well-controlled patients with NIDDM treated with diet or oral hypoglycemic agents (OHAs) do not require any special treatment before and during surgery. If fasting plasma glucose for the diet-treated patient is <7.8 mM, hourly blood glucose levels should be measured. Patients with this degree of glycemic control treated with an OHA may be given their medication and started on a glucose infusion at the usual time (~0700), although there is no agreement on this issue. Some investigators suggest stopping OHA treatment the evening before surgery, with chlorpropamide stopped 48–72 h preoperatively (11,12). However, there are no data examining this practice.

Treatment decisions for higher glucose levels are more controversial for this outpatient population. Perioperative insulin therapy should be considered when fasting or random blood glucose levels are >11.1 mM and definitely initiated when they are >13.9 mM. These values are chosen for the following reasons. First, fasting plasma glucose levels >11.1 mM tend to manifest absolute deficiency with respect to insulin secretion (107). Second, the renal threshold for glucose is ~10.0–11.1 mM in most patients with normal renal function (108). Osmotic diuresis with resulting water and electrolyte losses occur when this glucose level is exceeded. Finally, the data indicating impaired wound strength and wound healing with plasma glucose levels >11.1 mM need to be considered (3–6).

The decision to begin a variable-rate IVII or GIK infusion should be individualized depending on the patient and type of operative procedure. If an infusion is not started, subcutaneous regular insulin should be given. It is difficult to give a precise recommendation regarding the amount of insulin that should be administered to maintain euglycemia during and after the procedure. Four to 6 U of subcutaneous regular human insulin is a reasonable initial dose for a surgical patient not previously treated with insulin. More significant hyperglycemia (≥19.4 mM) should be treated with an IVII.

Malling et al. (109) recently studied two groups of patients with NIDDM during ambulatory surgical procedures. The patients were treated with either a GIK infusion or subcutaneous insulin followed by an infusion of glucose. Mean fasting glucose levels were <8 mM, and all subjects were taking OHA at home. There was no difference between the two groups in blood glucose levels and metabolic (β-hydroxybutyrate, lactate, glycerol, alanine) or hormonal (insulin, glucagon, growth hormone) parameters. Therefore, both of these treatment options are reasonable for this outpatient surgical population.

Patients with NIDDM previously taking insulin at home also have the option of receiving either an IVII or subcutaneous insulin during the perioperative period. The same principles of insulin strategy discussed for the patient with IDDM apply to this population. Furthermore, some of these patients are insulinopenic and thus are ketosis prone. Finally, for any patient who requires insulin therapy, there is less guesswork when an insulin infusion (vs. subcutaneous insulin) is used during the operation, particularly for patients at risk for developing postoperative nausea and vomiting.

Intracavitary surgery. Patients with NIDDM are insulin resistant (107,110). As previously discussed, surgical stress potentiates this insulin resistance, and larger dosages of insulin are required to prevent hyperglycemia. However, patients treated with diet alone, who have fasting plasma glucose levels of <7.9 mM, can be treated with observation alone. An insulin infusion should be initiated if the capillary glucose level is >11.1 mM during the operation. Alberti and Thomas (111) studied a group of patients with NIDDM who had a mean preoperative plasma glucose level of 8.9 mM. When these patients received no insulin (or OHA) therapy for their hyperglycemia their mean plasma glucose level 4 h postoperatively was 14.2 mM. These investigators concluded that all patients having major surgery who are taking an OHA should be started on an insulin-glucose infusion, because mean plasma glucose levels remained constant in the insulin-treated group (from 10.3 to 10.1 mM) 4 h after surgery compared with the increase noted above in the untreated group. In addition, β-hydroxybutyrate and FFA levels were lower in the insulin-treated group. Optimal management of these patients involves use of insulin and glucose infusions, starting with an insulin dose of 1.0 U/h. Patients with NIDDM who require insulin should be treated the same way during major surgery as the patient with IDDM.

Hyperosmolar hyperglycemic nonketotic coma has been reported as a postoperative complication in patients with NIDDM. This syndrome is characterized by marked hyperglycemia, plasma hyperosmolarity, profound dehydration, absence of ketoacidosis, and variable mental status changes. Due to the increased plasma glucose levels and insulin resistance present in coronary artery bypass operations, it is not surprising that this complication is much more likely to occur in this setting (45,91,112–114). Werb et al. (45) found mean ± SE plasma glucose levels of 31.8 ± 4.8 mM when nondiabetic patients were administered a cardioplegic solution (106 g glucose) during hypothermia. Seki (113) reported that the high mortality (42%) in patients with hyperosmolar hyperglycemic nonketotic coma undergo-

ing cardiac operations was due in part to the duration of time between the onset of polyuria and diagnosis (7.5 ± 0.8 days in nonsurvivors vs. 4.5 ± 0.8 days in survivors). Mortality was also found to be higher in patients without a known diagnosis of diabetes. In an earlier study, 66% of the patients had no history of diabetes (114). The dehydration in this group is further exacerbated by the routine postoperative use of loop diuretics. Therefore, diabetic patients undergoing coronary artery bypass surgery represent a special therapeutic challenge, and frequent perioperative blood glucose measurements are critical to avoid metabolic decompensation. Alberti and Marshall (14) suggest blood glucose monitoring every 15–30 min intraoperatively in patients with known diabetes.

EMERGENCY SURGERY

In the earlier study by Galloway and Shuman (75), 5% of all diabetic patients required emergency surgery. Of the operations performed, appendectomy was the most common major procedure (33% of all major procedures), and lower-extremity incision and drainage and lower-extremity amputation for infection were the most common minor procedures (39% of all minor procedures). Thirty-one percent of all patients were admitted with plasma glucose levels >11.1 mM, although data were not provided for the number of patients meeting criteria for DKA.

The first priority should be to fully evaluate the metabolic status of all diabetic patients scheduled for emergency surgery. Urine and serum acetone, electrolytes, plasma glucose, and pH should be sent to the laboratory. A saline infusion should be started, and if clinically indicated, a central venous catheter should be inserted. If DKA is confirmed, surgery should be delayed while standard treatment for this metabolic emergency is instituted (115). Campbell et al. (116) showed that 63% of diabetic patients presenting with DKA and severe abdominal pain and tenderness had disappearance of these symptoms after DKA was adequately treated. Episodes of this unexplained pain were reported in patients with IDDM who were <40 yr and markedly acidemic (serum bicarbonate <10 meq/L). Conversely, Wheelock et al. (74) point out that rebound abdominal tenderness, as seen in a surgical emergency, may be masked in the diabetic patient. The etiology of this phenomenon is not known, although it is probably due to diabetic neuropathy.

CONCLUSION

The hormonal environment during the perioperative period promotes protein and fat catabolism, and glucose production. The metabolic consequences of these processes may have devastating consequences in the diabetic patient. The basic principle of this review is that sufficient insulin and glucose are needed to prevent tissue breakdown. Unfortunately, there have been few carefully controlled studies comparing different treatment regimens for diabetic patients. Other than DKA and hyperosmolar hyperglycemic nonketotic coma, there is no direct evidence that normalization of these metabolic processes effects surgical outcome. Additional studies examining the effects of glycemic control in the perioperative period on wound healing, infection, and length of hospital stay are clearly needed.

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