USE OF INSULIN IN THE PERIOPERATIVE MANAGEMENT OF DIABETIC PATIENTS

Diabetli hastaların perioperatif tedavisinde insulin kullanımı

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Summary: *Diabetic patients undergoing surgery are at an increased risk for developing metabolic and endocrine changes leading to excessive hyperglycemia and ketonemia. The majority of patients who undergo major surgery will require insulin during the perioperative period in order to achieve good glycemic control, even if they may not have needed insulin therapy prior to surgery. Several regimens of insulin therapy are presented for optional use. To accommodate the rapid changes in metabolism during surgery and the recovery period, flexibility in administering insulin is needed; insulin administration by continuous intravenous infusion is an effective and safe method that provided this advantage. Continuous intravenous infusion of insulin is a treatment modality also useful in the management of diabetic patients in other rapidly changing clinical circumstances; technical details of this preferred method are given.*

Key Words: *Diabetes mellitus, Insulin therapy, Surgical interventions*

Özet: *Diabetli hastalar, cerrahi girişimler süresince, girişim sonucu metabolik ve endokrin değişimlerden ötürü, aşırı hiperglisemiye ve ketonemiye maruzdurlar. Büyük ameliyat geçirmekte olan diabetlilerin çoğunluğunda, ameliyat öncesi insulin tedavisi gerekmemiş olsa dahi, ameliyat içi ve sonrası kan şekerinin kontrolü için insulin öngörülür. Bu raporda, cerrahi girişimler süresince kullanılmağa uygun birkaç insulin tedavi rejimi gözden geçirilmektedir. İnsulin dozajının, ameliyat süresinde ve ameliyat sonrası hızla değişmesi beklenen metabolizma gerekçelerini karşılayacak şekilde değiştirilebilmesi istenir; bu avantajı temin edecek etkin ve emin metod, insulinin devamli olarak intravenöz yoldan verilmesidir. Intravenöz insulin infüzyon tedavi metodu, metabolizmanın hızla değişmesi beklenecek başka klinik durumlarda da kullanılabilir; tercihan kullanılması öngörülen bu metodun teknik detayları, bu bildiride verilmektedir.*

Anahtar Kelimeler: *Diabetes mellitus, Insulinle tedavi, Cerrahi girişimler*

Patients with diabetes are more likely to need surgery than the general population. Approximately 50% of diabetic patients will require at least one surgical procedure in their lifetime (1). In 1985, cardiovascular surgery accounted for approximately 11% of operations performed on diabetic patients in the United States, as compared to 4% in non-diabetic individuals. Five percent of diabetic patients versus 3% of nondiabetic persons require ophthalmologic surgical procedures (2). Patients with diabetes undergo about 40,000 amputations and more than 3,000 vitrectomies annually (2). Eleven to twelve percent of patients undergoing coronary bypass grafts have diabetes (2-4). Interestingly, 40 to 50% of diabetic patients were first diagnosed to have the disease at the time of admission for surgery (5).

In this article will be reviewed the importance of metabolic control in the perioperative period in diabetic patients, the indications for insulin therapy, and various methods for insulin administration to achieve good glycemic control. Particular emphasis is placed on the use of continuous intravenous infusion of insulin, which has emerged as a safe and effective method to

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maintain glucose homeostasis during a period of rapidly changing insulin requirements.

COMPLICATIONS OF UNCONTROLLED HYPERGLYCEMIA

Submitting a diabetic patient to surgery without first achieving reasonable control of blood glucose levels invites problems during and following surgery. Around the time of surgery, there is an increased incidence of diabetes-specific complications, such as ketoacidosis and the nonketotic hyperosmolar state. In addition, persistently elevated blood glucose levels (over 240 mg/dl) are associated with an increased risk of bacterial and fungal infections, and with impaired wound healing (6-10).

During the perioperative period, urinary tract infection, pneumonia, and other systemic infections tend to occur more frequently in diabetic patients than in the general population (10-12). In a review of nearly 24,000 surgical cases, the incidence of wound infection in clean incisions was found to be 11% in diabetic patients, and 2% in patients without diabetes (13). A retrospective study of 241 diabetic patients showed a highly significant positive correlation between the frequency of infections and the mean plasma glucose levels (10). Hyperglycemia causes abnormalities in leukocyte function, such as impaired chemotaxis and phagocytic activity, and reduced bactericidal activity against certain invading organisms (10,14,15). When hyperglycemia is corrected with insulin therapy, impairment of phagocytosis, leukocyte migration, and adherence to vascular endothelium are corrected (16).

In diabetic animals with hyperglycemia, wound healing was impaired, because of delayed formation of collagen and granulation tissue, and decreased tensile strength of deep surgical wounds; wound healing was normal when blood glucose levels were kept close to normal (17). In diabetic patients, improvement of blood glucose levels with insulin therapy also enhanced the rate of wound healing (6,7,16).

Thus, glucose control during the perioperative period is desirable, not only to prevent acute decompensation of diabetes in conjunction with surgery, but also to maintain intact host defense mechanisms and to enhance wound healing.

METABOLIC AND ENDOCRINE RESPONSES TO SURGERY

Anabolism and catabolism are normally balanced through an interplay of hormones (18-20). Insulin is a major anabolic hormone that stimulates glucose uptake by muscle and adipose tissue, promotes hepatic glycogen formation, enhances fatty acid transport and triglyceride synthesis, and increases amino-acid transport and protein synthesis in muscle. In normal adults, pancreatic islet beta-cells secrete approximately 50 units of insulin daily at rates regulated primarily by the plasma glucose level. In the postabsorptive (fasting) state, insulin is secreted at a rate of approximately one unit per hour.

Catabolic hormones (glucagon, cortisol, and catecholamines), secreted in the fasted state, oppose insulin action by stimulating hepatic glycogenolysis and gluconeogenesis, decreasing glucose utilization in peripheral tissues, and increasing fat and protein breakdown (18-24). The stress of anesthesia and surgery promotes the release of these catabolic hormones (20-22). The magnitude of the catabolic response varies with the condition necessitating surgery, the duration of surgery, the severity of trauma related to surgical manipulation, and the type of preexisting diabetes. Importantly, in the diabetic patient, catabolic influences dominate, due to insufficient activity of the anabolic hormone insulin. The result is excessive hyperglycemia and increased protein breakdown.

MANAGEMENT OF THE DIABETIC SURGICAL PATIENT

Metabolic control prior to surgery: Perioperatively, maintenance of blood glucose concentrations between 120 mg/dl and 200 mg/dl is desirable, in order to reduce problems associated with fluid and electrolyte disturbances, infections and wound healing. Establishment of good control just prior to surgery will reduce the hyperglycemic impact of anesthesia and surgery; intraoperative management of hyperglycemia is thus simplified.

One may consider hospitalizing diabetic patients, who are not in good metabolic control, two to three days before surgery to optimize blood glucose concentrations under controlled circumstances (19). The high costs involved with hospitalization limit this option; nevertheless, patients undergoing major surgery, such as coronary artery bypass graft or renal transplant, may be admitted at least one day prior to the surgery. Currently, most diabetic patients are admitted on the morning of surgery; self-monitoring of blood glucose has made it easier to avoid preoperative hyperglycemia on an outpatient basis. In patients who receive insulin in the preoperative period, the surgery should be scheduled early in the day, to avoid prolonging the catabolic state (fasting) and to minimize the risk of preoperative hypoglycemia resulting from withholding food.

Indications for insulin in the perioperative management of the diabetic patient: Insulin must be administered around the time of surgery in all patients with insulin-dependent diabetes mellitus (IDDM), and in patients with noninsulin-dependent diabetes mellitus (NIDDM) requiring insulin for maintenance therapy (18-20). Patients with NIDDM, who are poorly controlled (fasting blood glucose >180 mg/dl, glycosylated hemoglobin more than 2% above the upper limit of normal) on diet alone, or on diet plus oral hypoglycemic drugs, should also receive insulin therapy in the perioperative period. NIDDM patients who are well-controlled on diet and/or oral hypoglycemic agents, but are to undergo major surgery (invasion of a body cavity, particularly cardiopulmonary bypass surgery or organ transplant), should also be considered candidates to receive insulin in the perioperative period. NIDDM patients, who are adequately controlled (fasting blood glucose <180 mg/dl, glycosylated hemoglobin normal or slightly above normal) on diet and/or oral hypoglycemic drugs, generally do not require insulin treatment when undergoing minor surgery lasting less than two hours, not involving body cavity invasion, and when general anesthesia is not planned for the procedure (18-20).

The success of insulin therapy in the perioperative period relies on monitoring of blood glucose levels several times daily. This is best accomplished at bed-side, by obtaining capillary blood by piercing the finger with a microlancet, placing a drop of blood on a glucose oxidase reagent strip, and reading the glucose value in a glucose meter. These devices are inexpensive, accurate and widely available.

"Conventional" perioperative insulin regimens in insulin-treated patients: Preferences for the route of administration of insulin in the perioperative period are highly variable, particularly in regards to subcutaneous versus intravenous insulin regimens (25-27). Many clinicians seem to use subcutaneous insulin regimens simply out of habit, or because it is the method traditionally used in a particular institution. A variety of regimens have been published for the administration of insulin in preparation for surgery (18-20,28,29).

In patients using long-acting (ultralente) insulin, switching to an intermediate-acting insulin (NPH or lente) three days before surgery may be desirable. This precaution may be less warranted with human ultralente insulin, because its duration of action is shorter than that of long-acting animal insulins (ultralente or protamine-zinc) (30). The traditional approach in a patient customarily taking an intermediate-acting insulin is to administer that insulin subcutaneously (s.c.) at about 30% to 50% of the patient's usual morning dose, on the morning of surgery. The rationale for using a lower preoperative dose of an intermediate-acting insulin is to reduce the risk of afternoon hypoglycemia, in case the surgery is delayed. Along with this, an intravenous infusion of 5% dextrose is started at a rate of 100 ml per hour (5 grams glucose per hour). Blood glucose is monitored during and after surgery, and excessive hyperglycemia (>200 mg/dl) is treated with supplemental doses of regular crystalline insulin given s.c. every 4 to 6 hours, using a "sliding scale" based on prevailing capillary blood levels of glucose (18,31-33). If the patient is at risk of hypoglycemia (<80 mg/dl), the rate of glucose infusion may be increased. The remainder of the daily dose of the intermediate-acting insulin may be given upon completion of surgery; thereafter, regular crystalline insulin may be given as needed, according to a sliding scale (32). Alternatively, the remainder of the customary dose of intermediate-acting insulin may be omitted, and only short-acting insulin be given subcutaneously, as needed according to a sliding scale.

There are several disadvantages to using subcutaneous intermediate-acting insulin around the time of surgery. First, the regimen is not flexible enough to accommodate rapid changes in insulin requirements during and after surgery. Second, the rate of insulin absorption from subcutaneous tissue is variable, unpredictable, and affected by factors such as the site of injection, regional blood flow, temperature, mobility of the patient, and the dose injected (34,35). Hemodynamic changes associated with surgery can further alter the rate of insulin absorption, inducing wide fluctuations in blood glucose levels. Third, the depot effect of intermediate-acting insulins increases the risk for hypoglycemia, especially if the period of fasting is prolonged.

Prescribing short-acting, regular crystalline insulin, to be given several times daily according to prevailing levels of blood glucose (sliding scale), though considerably more flexible than using intermediate-acting insulins, also has disadvantages. These regimens allow the blood glucose to rise to undesirable levels before a dose of regular insulin is given. In addition, many physicians habitually employ a preconceived sliding scale in most of their patients, ignoring the fact that sensitivity to insulin will be different among diabetic patients, and that the sensitivity will change even in the same patient during the perioperative period. Thus, sliding-scale regular insulin regimens often result in a roller coaster-like blood glucose profile (18,20,33).

Continuous intravenous infusion of insulin (the preferred regimen): Administering short-acting, regular crystalline insulin intravenously, as a continuous infusion, is an effective method to achieve and maintain good control of blood glucose during periods of rapidly changing metabolism, such as the perioperative period. This approach is gradually replacing the conventional subcutaneous methods of insulin administration. Two slightly different regimens for intravenous insulin administration have been validated (18-20,36).

One method involves infusing insulin (1-2 U/h) and 5% dextrose (100 ml/h, or 5 grams glucose per hour) as two separate solutions (18-20). The glucose solution usually contains potassium (e.g. 40 mEq/L KCl), because influx of potassium into cells increases with the administration of insulin and glucose. This is a flexible regimen, in that the flow rate of each solution can be adjusted independently. The insulin infusion rate is regulated according to frequently measured capillary blood glucose levels. One concern with this method is that if one of the infusion lines gets blocked, dislodged, or speeds up accidentally, the patient is at risk for developing hypoglycemia or hyperglycemia. Any such risks can be minimized by using infusion pumps.

The second method involves combining glucose, insulin, and potassium ("GIK") in a single solution for intravenous infusion. Generally, 10 units of regular crystalline insulin and 20 to 40 mEq of potassium chloride are added to 1000 ml of 5% dextrose, and the solution is infused at a rate of 100 ml per hour, to provide glucose 5 g/h, potassium 2 to 4 mEq/h, and insulin 1 U/h. Adjustments in the flow rate are based on frequently monitored blood glucose levels. The disadvantage of this method is that the insulin infusion rate cannot be adjusted independently, without discarding an entire bag of fluid. For this reason, the GIK infusion may not be the preferred method of insulin delivery when blood glucose levels tend to fluctuate widely, as is often observed in IDDM patients undergoing lengthy surgical procedures. In NIDDM patients undergoing short surgical procedures, the insulin requirements usually do not show marked variations; GIK may be a viable option in this situation (18-20).

Experience is a contributing factor in selecting the method of infusing insulin and glucose separately or in combination. The physician may choose one of these methods based on an individual (or more likely institutional) preference, and use that method preferentially, to gain experience and confidence. The success of either method depends on frequent blood glucose measurements. A bedside blood glucose monitoring system is, therefore, necessary. There is no consensus regarding the frequency of bedside glucose monitoring. One may consider monitoring every hour for the first four hours of starting the infusion, and, once stabilized, reducing the frequency to every two hours until the time of surgery; during surgery the frequency of monitoring may be increased again to hourly (18,20). Serum potassium levels should be checked 6 to 8 hours after starting the insulin infusion, and monitored daily thereafter, as needed.

Intravenous insulin infusion regimens for use in the perioperative period are designed on the premise that the patient will also be receiving glucose intravenously, as the essential nutrient at a time no food is taken by mouth. Glucose acts as the source of energy needed for basal metabolism, as well as for the increase in metabolism caused by the stress of general anesthesia and surgery. If glucose is not given, protein breakdown would increase in an effort to provide substrate for gluconeogenesis, thus bringing wound healing into jeopardy. In addition, glucose, infused at the same time with insulin, reduces the risk of hypoglycemia.

The above recommendations for the amounts of insulin and glucose to be administered are intended to be used as a guideline, in the treatment of an average adult patient. More precise estimates for adult and pediatric patients may be derived from basic knowledge on the physiology of glucose and insulin kinetics. In the postabsorptive (fasting basal) state, hepatic glucose production is 70-150 milligrams per kilogram body weight per hour (mg/kg/h), or 1.7-3.6 grams per kilogram body weight per day (g/kg/day), which equals the glucose disposal rate (peripheral glucose uptake), so that blood glucose level remains constant. To maintain this balance, in a nonobese person (obesity causes insulin resistance), the pancreas secretes insulin at the rate of 7-15 milliunits/kg/h. When the stress of general anesthesia and surgery were to be superimposed on the postabsorptive state, insulin secretion rate would have to increase, to counteract the effects of stress hormones (glucagon, epinephrine, cortisol...) that stimulate gluconeogenesis and/or glycogenolysis. In a diabetic patient with little or no insulin-secretory capacity, this would reflect itself as an increase in the therapeutic insulin requirements. Thus, irrespective of whether the surgical patient has diabetes, or requires insulin therapy or not, to prevent protein breakdown during a prolonged period of no oral food intake, glucose should be administered intravenously in amounts of about 1.7-3.6 g/kg/day (or 120-250 g/day in a 70-kg adult). In the diabetic patient requiring insulin therapy, prior to the induction of general anesthesia and surgery, the infusion of glucose would be accompanied by intravenous infusion of insulin, at the rate of about 7-15 milliunits/kg/h (or 0.5 to 1 unit/h in a 70-kg adult). These amounts would have to be increased as much as two- to three-fold during the stressful periods of general anesthesia and surgery, and possibly in the immediate postoperative period (18-20,28,37-39). As a general guideline, in an adult diabetic patient, on an hourly basis, for each gram of glucose administered, 0.3 to 0.4 unit of insulin may be infused intravenously (19,20,37-39). Thus, a patient receiving an intravenous infusion of 5% glucose solution at the rate of 100 ml/h (5 g/h) may require intravenous insulin, infused at the rate of 1.5 to 2 units per hour.

Intravenous infusion of insulin, which begins preoperatively and continues during surgery, should be extended into the postoperative recovery period, as it is the most flexible method for controlling blood glucose in this phase of the surgery as well (19,20,36). As the patient's general condition changes, the insulin sensitivity will change; therefore, the infusion rate can be adjusted, based on blood glucose levels monitored at the bedside. The infusion may be stopped when the first meal is eaten and tolerated. Thereafter, patients who were on maintenance insulin therapy prior to surgery, may return to the preoperative insulin dosage and regimen. In that situation, the first subcutaneous dose may be administered about

30 minutes prior to the first postoperative meal, and the intravenous insulin infusion terminated. NIDDM patients previously treated with oral hypoglycemic drugs may resume that therapy, if blood glucose levels remain less than 180 mg/dl after termination of the insulin infusion. If blood glucose level exceeds 180 mg/dl at the time the patient starts eating, regular insulin may have to be given subcutaneously before each meal, following a sliding scale, until stable blood glucose values are obtained.

Bolus intravenous injections of insulin: The administration of regular crystalline insulin by intermittent, intravenous bolus is an old method, also intended to meet the needs of rapidly changing body metabolism (39,40). When given intravenously, insulin has a short duration of action of approximately 20 minutes. Intermittent administration causes a roller-coaster type of effect, predisposing the patient to the development of hypoglycemia alternating with hyperglycemia. In contemporary medicine, there is no place for the administration of large intravenous bolus doses of insulin.

CLINICAL TRIALS COMPARING CONVENTIONAL WITH INTRAVENOUS INSULIN THERAPY

Major surgery: In several studies, the outcomes of intravenous insulin infusion therapy were compared with those of subcutaneous administration (29,31,36-38). In 1977, Taitelman and associates (31) studied the effects of insulin given s.c. or intravenously in 23 insulin-requiring diabetic patients undergoing orthopedic surgery. Ten patients required 20 units or less of NPH insulin per day for their preoperative management (group A), and 13 required more than 20 units per day (group B). In each group, the patients were randomized either to receive insulin by continuous intravenous infusion (Group A at 1 U/h, Group B at 2 U/h), or to receive two-thirds of their preceding daily NPH dose s.c. immediately before surgery. The patients were followed for up to eight hours after surgery; all patients received 5% dextrose at a rate of 125 ml/h. Rates of infusion of insulin and glucose were adjusted, as indicated by blood glucose measurements. In Group A, glucose levels did not differ significantly between patients receiving insulin s.c. or by intravenous infusion, whereas in Group B better glucose control was achieved with intravenous infusion (2 U/h). However, two of the eight patients receiving insulin intravenously at a rate of 2 U/h developed hypoglycemia and the infusion rate had to be decreased to 1 U/h. In many patients, the preoperative blood glucose levels were suboptimal (92 to 406 mg/dl in the group receiving s.c. insulin, and 148 to 358 mg/dl in the group receiving intravenous insulin), making interpretation of the results difficult. This study indicates that a flexible infusion rate of insulin is desirable in order to use the intravenous infusion method to full advantage.

In a controlled trial, Goldberg et al (29) evaluated 12 insulin-requiring diabetic patients undergoing abdominal surgery under general anesthesia. The patients were randomly assigned to receive insulin either by intravenous infusion at 1 U/h, or by s.c. injection of one-half of the patient's usual insulin dose, given on call to the operating room. All patients received 5% dextrose intravenously, administered at variable rates throughout the surgery. During the intraoperative period, glucose levels rose to 345+31 mg/dl and 390+80 mg/dl in the continuous infusion and the preoperative s.c. insulin groups, respectively; the difference was not statistically significant. These results are not conclusive, however, because the number of patients was small, insulin was infused at a fixed rate, glucose was infused at arbitrary rates, and lactate-containing solutions rather than glucose were sometimes given.

Several investigators have shown better glucose control with intravenous insulin infusion than with conventional subcutaneous regimens (36,37-39). The GIK solution was used for infusion in most studies. One of the earliest reports was by Alberti and Marshall (36), which showed better blood glucose control with a GIK infusion than with subcutaneous insulin regimens. Thomas et al (37) conducted a randomized study of 27 IDDM patients undergoing major surgery. Eleven patients were randomly assigned to the conventional treatment group, and received one-half to threequarters of the usual morning insulin dose s.c., followed by an intravenous glucose infusion. Twelve patients were randomly assigned to receive GIK treatment, which was continued for 6 to 21 hours; four of these patients were further studied for 72 hours of GIK infusion. The results showed a significant difference in blood glucose control between the conventional s.c. and the GIK groups. Patients treated conventionally with s.c. insulin showed an increase in plasma glucose concentrations from 167 mg/dl to 268 mg/dl four hours after the operation, while patients receiving the GIK infusion showed little change in glucose levels (186 mg/dl to 198 mg/dl). All subsequent postoperative blood glucose levels were lower in the infusion-treated group than in the conventional subcutaneous insulin group; the difference was most marked at 72 hours.

In a mixed sample of 30 IDDM and NIDDM patients undergoing major surgery, Pezzarossa and associates (38) evaluated the effectiveness of subcutaneous versus intravenous insulin administration. The patients were divided into two groups that were similar in age, sex distribution, type of diabetes, and type of surgical procedures. The subjects were randomly assigned to receive an intravenous insulin infusion or regular insulin given s.c. every four hours. In both groups, the insulin dose was modified only if blood glucose level was greater than 180 mg/dl or less than 120 mg/dl, with a target value of 140 mg/dl. Patients receiving intravenous insulin infusion had closer to normal blood glucose values during the intraoperative period, and the total insulin requirement, expressed as the insulin-to-glucose ratio, was significantly lower (0.18±0.30) than that of the s.c. insulin group (0.27±0.30, $p < 0.05$). Similar findings were reported in other studies; during major surgery, better glycemic control was achieved with intravenous insulin infusion than with conventional s.c. regimens (39).

Minor surgery: Christiansen et al (40) compared GIK with conventional s.c. insulin in IDDM patients having minor surgery under general anesthesia. The group receiving GIK infusion had significantly better blood glucose control during the infusion period, as well as during the first and second postoperative days, than the group receiving conventional subcutaneous insulin therapy.

NIDDM patients well controlled on diet or oral hypoglycemic agents usually do not require insulin during minor surgical procedures. In one prospective trial, 43 NIDDM patients (fasting blood glucose <170 mg/dl) were managed without insulin during minor surgical procedures not requiring general anesthesia (41). During the postoperative period, 40 (93%) of the patients had blood glucose levels that were well within the acceptable range (90 to 200 mg/dl). Oral hypoglycemic drugs were omitted on the morning of the operation, and fluids containing glucose or lactate were avoided. In another study, Thompson et al (42) compared the metabolic response to minor surgery in NIDDM patients treated with or without a GIK infusion, with that in a control group of nondiabetic patients. The patients with diabetes were randomly allocated to receive GIK infusion or were managed without insulin. Oral hypoglycemic drugs (all short-acting) were omitted on the morning of surgery. Anesthesia and surgery did not have a significant effect on glucose, fatty acids, glucagon, insulin, or cortisol concentrations in the control group. Diabetic patients not given GIK similarly showed no changes in blood glucose, plasma nonesterified fatty acids, 3-hydroxybutyrate, glycerol, serum insulin, or plasma glucagon. In diabetic patients treated with GIK, the serum concentrations of insulin increased, while the concentrations of nonesterified fatty acids, glycerol, and 3-hydroxybutyrate were lower than those in the control group. Although blood glucose levels were lower in patients receiving GIK than in patients not receiving GIK, the difference was significant only at two hours postoperatively. Thus, moderately well-controlled NIDDM patients undergoing minor surgery may do well metabolically without receiving insulin therapy perioperatively, provided that glucose-containing fluids are not given.

SURGICAL CIRCUMSTANCES ASSOCIATED WITH EXCESSIVE INSULIN RESISTANCE

Cardiopulmonary bypass operation: Cardiopulmonary surgery may have deleterious effects on the metabolic control of diabetic patients, beyond those that occur in conjunction with major surgery. Though not defined precisely, several factors may be operative. Extracorporeal circulatory assistance requires large volumes of fluids to be administered, and the pump is often primed with glucose-containing solutions. Induced hypothermia may cause insulin resistance. Adrenergic drugs often used in these procedures oppose the actions of insulin. In combination, these factors may lead to excessive increases in blood glucose levels (42,43). Marked increases have been observed in blood levels of catecholamines and cortisol; in patients not on insulin treatment, serum insulin levels were found to be inappropriately low (42,43). The magnitude of insulin resistance in coronary artery bypass surgery is such that patients may require insulin doses that are 3- to 5-fold higher than those needed for other types of major surgery (19,32,36). In these patients, continuous intravenous infusion of insulin facilitates rapid adjustments in dosage based on frequent measurements of blood glucose (e.g. every 15 to 30 minutes) (43).

Other situations: Conditions associated with insulin resistance may coexist in the diabetic surgical patient, causing increased perioperative insulin requirements for insulin. These conditions include obesity, hepatic disease, severe infection, steroid therapy, and patients undergoing renal transplant surgery (18-21). Adjustments in the dose of insulin should be customized to meet individual requirements in these circumstances. Patients who are obese or who have significant liver disease may be given 1.5 times the usual insulin doses (0.4 to 0.6 units insulin per gram of intravenously administered glucose) (18-20). For patients with severe infection, those receiving steroid therapy or undergoing renal transplant surgery, a two-fold increase in the dose of insulin may be necessary (0.5 to 0.8 units insulin per gram of intravenously administered glucose) (18-20). As with cardiopulmonary bypass surgery, insulin delivered by continuous intravenous infusion allows for rapid adjustments in dose, based on frequent blood glucose measurements.

Emergency surgery: In diabetic patients, conditions requiring emergency surgery are invariably associated with major metabolic changes and deterioration of control of blood glucose. Ketoacidosis and nonketotic hyperosmolar state are frequently encountered under these circumstances, and may necessitate postponement of surgery until the life-threatening metabolic problem is brought under control (44). The first priority, therefore, is to assess glucose control, hydration, and acid-base balance of the patient. Depending on the nature of the emergency that requires surgical intervention, the stress of the condition is likely to induce insulin resistance. Therefore, increased insulin requirements during the perioperative period must be anticipated. A flexible insulin regimen, such as continuous intravenous infusion, would facilitate the establishment and maintenance of adequate metabolic control.

CONCLUSIONS

Surgery, especially if performed under general anesthesia, produces metabolic and endocrine changes and variable degrees of insulin resistance; these changes occur in a short period of time and at a rapid rate. In a diabetic patient, excessive hyperglycemia, lipolysis, and ketogenesis during surgery can pose major risks. Most diabetic patients undergoing major surgery will need insulin therapy in the perioperative period. Continuous intravenous infusion is an effective way of administering insulin to accommodate the rapid metabolic/endocrine changes that occur during surgery and the recovery period. The availability and use of infusion pumps in all inpatient care areas has made it safer to deliver insulin by continuous infusion, without the need for a critical care facility. Adjustments in the infusion rate result in rapid changes in blood levels of insulin, thus permitting prompt correction of excesses or deficiencies in insulin availability.

Frequent monitoring of blood glucose levels, preferably by using suitable equipment at the patient's bedside, is mandatory, and will secure safe and effective use of insulin by intravenous infusion. Continuous intravenous infusion of glucose in conjunction with insulin infusion adds further to the safety of this method, while providing the fuel for basic metabolism.

REFERENCES

1. *Root HF. Pre-operative care of the diabetic patient. Postgrad Med 1966; 40:439-43.*
2. *Sinnock P. Diabetes in America (National Diabetes Data Group). In: Harris MI, Hammon RF (eds), US Department of Health and Human Services. Washington 1985, pXXVI-I-II.*
3. *Solomon NW, Page US, Okies JE, et al. Diabetes mellitus and coronary artery bypass. Short-term and long-term prognosis. J Thoracic Cardiovasc Surg 1985; 85:264-71.*
4. *Johnson WD, Pedraza PM, Kayser KL. Coronary artery surgery in diabetics: 261 consecutive patients followed four to seven years. Am Heart J 1982;104: 823-7.*
5. *Molitch ME, Reichlin S. The care of the diabetic patient during emergency surgery and post-operatively. Orthop Clin North Am 1978; 9:811-24.*
6. *McMurry JF. Wound healing with diabetes mellitus: better glucose control for better healing in diabetes. Surg Clin North Am 1984; 64:769-78.*
7. *Goodson WH, Hunt TK. Wound healing with diabetes mellitus. Surg Clin North Am 1984; 64:762-8.*
8. *Hjortup A, Sovensen C, Dyremose E, et al. Influence of diabetes mellitus on operative risk. Br J Surg 1985; 72:783-5.*
9. *Farrington M, Webster M, Fenn A. Study on cardiothoracic wound infection at St. Thomas Hospital. Br J Surg 1985; 72:759-62.*
10. *Rayfield EJ, Ault MJ, Keusch GT, et al. Infection and diabetes: the case for glucose control. Am J Med 1982; 72:439-50.*
11. *Larkin JG, Frier BM, Ireland JT. Diabetes mellitus and infection. Postgrad Med J 1985; 61:233-7.*
12. *Lilienfeld DE, Vlahov D, Tenney JH, et al. Obesity and diabetes as risk factors for postoperative wound infections after cardiac surgery. Am J Infect Control 1988; 16:3-6.*
13. *Cruse PJ, Foord R. A 5-year prospective study of 23,649 surgical wounds. Arch Surg 1973; 107:206-10.*
14. *Bagdade JD. Phagocytic and microbicidal function in diabetes mellitus. Acta Endocrinol 1976; 83 (Suppl 205):27-34.*
15. *Nolan CM, Beaty HN, Bagdade JD. Further characterization of the impaired bactericidal function of granulocytes in patients with poorly controlled diabetes. Diabetes 1978; 27:889-94.*
16. *Goodson WH, Hunt TK. Studies of wound healing in experimental diabetes mellitus. J Surg Res 1977; 22:221-7.*
17. *Weringer EJ, Kelso GM, Tamai IY, et al. The effect of insulin, 2-deoxyglucose-induced hyperglycemia, and starvation on wound healing in normal mice. Diabetes 1981; 30:407-10.*
18. *Hirsch MD, McGill JB, Cryer PE, et al. Perioperative management of surgical patients with diabetes mellitus. Anesthesiology 1991; 74:346-59.*
19. *Alberti KGMM, Gill GV, Elliot MJ. Insulin delivery during surgery in the diabetic patient. Diabetes Care 1982; 5 (Suppl 1):65-77.*
20. *Gavin LA. Perioperative management of the diabetic patient. Endocrinol Metab Clin North Am 1992; 21:457-75.*
21. *McMohan M, Gerich J, Rizza R. Effect of glucocorticoids on carbohydrate metabolism. Diabetes Metab Rev 1988; 4:17-30.*
22. *Clutter WE, Bier DM, Shah SD, et al. Epinephrine plasma metabolic clearance rates and physiological thresholds for metabolic and hemodynamic actions in man.*

J Clin Invest 1980; 66:94-101.

23. *Allison SP, Tomlin PJ, Chamberlin MJ. Some effects of anesthesia and surgery on carbohydrate and fat metabolism. Br J Anaesth 1969; 41:588-93.*
24. *Foster KJ, Alberti KGMM, Binder C, et al. Lipid metabolites and nitrogen balance after abdominal surgery in man. Br J Surg 1979; 66:242-5.*
25. *Clark JDA, Hartog M. Management of diabetes in surgery: a survey of current practice by anesthesists. Diabet Med 1992; 9:271-4.*
26. *Thai AC, Husband DJ, Gill GV, et al. Management of diabetes during surgery: a retrospective study of 112 cases. Diabet Med 1984;10:65-70.*
27. *Dunnet JM, Holman RC, Turner RC, et al. Diabetes mellitus and anesthesia: a survey of the perioperative management of the patient with diabetes mellitus. Anesthesia 1988; 43:538-42.*
28. *Hirsch IB, Farkas-Hirsch R, Skyler JS. The use of intensive insulin therapy in the treatment of diabetes mellitus. Diabetes Care 1990; 13:1265-83.*
29. *Goldberg NJ, Wingert TD, Levin Sr, et al. Insulin therapy in the diabetic surgical patient: metabolic and hormonal response to low dose insulin infusion. Diabetes Care 1981; 4:279-84.*
30. *Holman RR, Steemson J, Darling P, et al. Human ultralente insulin. Br Med J 1984; 288:665-8.*
31. *Taitelman U, Reece EA, Bessman AN. Insulin in the management of the diabetic surgical patient: continuous intravenous administration versus subcutaneous administration. JAMA 1977; 237:658-60.*
32. *Rossini AA, Hare JW. How to control the blood glucose level in the surgical diabetic patient. Arch Surg 1976; 3:945-9.*
33. *Shade DS. Surgery and diabetes. Med Clin North Am 1988; 72:531-43.*
34. *Galloway JA, Apradlin CT, Nelson RL, et al. Factors influencing the absorption, serum insulin concentration, and glucose responses after injections of regular insulin and various insulin mixtures. Diabetes Care 1981; 4:366-76.*
35. *Hildebrant P, Sestoft L, Nielson SL. The absorption of subcutaneously injected short-acting soluble insulin. Influence of injection technique and concentration. Diabetes Care 1983; 6:459-62.*
36. *Alberti KGMM, Marshall SM. Diabetes and surgery. In: The Diabetes Annual/4, Alberti KGMM, Krall LP (eds), New York, Elsevier 1988.*
37. *Thomas DJB, Platt HS, Alberti KGMM. Insulin-dependent diabetes during the perioperative period. Anesthesia 1984; 39:629-37.*
38. *Pezzarossa A, Taddei F, Cimicchi MC, et al. Perioperative management of diabetic subjects: subcutaneous versus intravenous insulin administration during glucose-potassium infusion. Diabetes Care 1988; 11:52-8.*
39. *Nel CJC, deWall JM, Steyn AF. The perioperative management of diabetes. S Afr J Surg 1980; 19:107-112.*
40. *Christiansen CL, Schurizek BA, Malling B, et al. Insulin treatment of the insulin-dependent diabetic patient undergoing minor surgery. Anesthesia 1988; 43:533-7.*
41. *Husband DJ, Thai AC, Alberti KGMM. Management of diabetics during surgery with glucose-insulin-potassium infusion. Diabet Med 1986; 3:69-74.*
42. *Thompson J, Husband DJ, Thai AC, et al. Metabolic changes in the non-insulin dependent diabetic undergoing minor surgery: effect of glucose-insulin-potassium infusion. Br J Surg 1986; 73:301-4.*
43. *Elliot MJ, Gill GV, Home PD, et al. A comparison of two regimens for the management of diabetes during open-heart surgery. Anesthesiology 1984;60:364-8.*
44. *Barrett EJ, DeFronzo RA. Diabetic ketoacidosis: diagnosis and treatment. Hosp Pract 1984;19:89-104.*