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Review

Parenteral Nutrition in Patients with Diabetes Mellitus: Theoretical and Practical Considerations

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ABSTRACT. It is estimated that there are 11 million diabetics in the United States. Increasing recognition of the importance of nutrition in clinical medicine coupled with the frequent hospitalizations of the diabetic patient has heightened interest in their nutritional therapy. Patients with diabetes mellitus exhibit many abnormalities in the regulation of carbohydrate metabolism which may be accentuated during illness as part of the metabolic response to injury. An understanding of the effect of injury/illness, parenteral nutrition, and diabetes mellitus on carbohydrate metabolism is essential for the development of a rational approach to the initiation and maintenance of nutritional support in the diabetic patient. (*Journal of Parenteral and Enteral Nutrition* **13**:545–553, 1989)

Diabetes mellitus is a disorder of metabolism caused by an absolute (insulin-dependent diabetes mellitus, IDDM, Type I) or a relative (noninsulin-dependent diabetes mellitus, NIDDM, Type II) lack of insulin. Relative insulin deficiency can result from a diminution in insulin secretion, from an impairment in insulin action, or from a combination of both factors. The metabolism of all fuels (carbohydrate, fat, protein, and ketone bodies) is altered in this disease. It is estimated that there are 11 million diabetics in the United States.[1] In this country, comparing diabetics to nondiabetics, blindness is 29 times more frequent, renal failure is 17 times more frequent, amputation is five times more frequent, and coronary artery disease and stroke are two to six times more frequent.[2–5] The increasing recognition of the importance of nutrition in clinical medicine, combined with the significant prevalence of protein-calorie malnutrition (nearly 50%) among hospitalized patients[6, 7] and the frequent hospitalizations of the diabetic have heightened interest in their nutritonal therapy.

Total parenteral nutrition (TPN) can be a safe and effective form of nutritional support in the diabetic person. The New England Deconess Hospital, with 489 beds, is the in-patient facility for the Joslin Clinic which specializes in the care of the diabetic patient. The Nutrition Support Service that provides TPN for 5% of patients at this institution has thereby gained an extensive experience in providing nutritional support for this group of patients. Based on our experience with this novel hospital population, a review of various aspects of clinical nutrition in the diabetic individual will be presented.

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REGULATION OF CARBOHYDRATE METABOLISM

Homeostatic Mechanisms

In nondiabetic subjects, the plasma glucose concentration is closely regulated in both the postabsorptive (6–14 hr after a meal) and the postprandial period. Prior to meal ingestion, plasma glucose is primarily derived from the liver since cellular glucose release requires glucose-6-phosphatase, an enzyme present in significant amounts only in the liver and kidney. Endogenous production results both from glycogenolysis (the breakdown of glucose stored as glycogen) and from gluconeogenesis (the formation of glucose from precursors).[8–10] Following a meal, circulating glucose can be derived from dietary carbohydrate in addition to its endogenous production. Under certain conditions, some of the glucose load is converted to three-carbon intermediates by peripheral tissues before entering the liver glycogen pool.[11–13] This has been called the indirect pathway of glycogen synthesis in contradistinction to the direct uptake, phosphorylation, and incorporation of glucose into glycogen by the liver.

The circulating glucose taken up by the cell is either further metabolized or stored. Glucose may undergo glycolysis to pyruvate (that can be further oxidized for ATP production), or be converted to other substrates, as lactate and alanine, (which can be transported to other tissues), or to fatty acids (which can be stored as triglyceride). The first intracellular reaction involving glucose is its phosphorylation to glucose-6-phosphate. This re-

action in the liver is controlled by two enzymes, hexokinase and glucokinase. The activity of hexokinase is stable under most conditions. The activity of glucokinase, on the other hand, increases with refeeding or insulin administration. Euglycemia is maintained because the rate of glucose release by the liver (glucose production) equals the combined rate of glucose uptake (glucose utilization) by the liver, brain, and peripheral tissues. These rates average 2 mg/kg of body weight/min in the nondiabetic subject in the postabsorptive period, or 200 g/day in a 70-kg person.

The isotope dilution technique, in combination with the glucose clamp, has been extensively employed to measure glucose turnover (rates of hepatic glucose production and whole body glucose utilization) in clinical research. The isotope dilution technique uses isotopically labeled glucose to trace rates of glucose production and glucose utilization. In addition, as discussed in more detail later, the biological effect of insulin can be directly assessed by examining its effect on hepatic glucose production and on whole body glucose utilization. The combination of the isotope dilution method, which estimates oxidation of plasma glucose, with indirect calorimetry, which estimates oxidation of intra-and extracellular glucose, is useful in defining rates of glucose oxidation.

It is helpful to first review the regulation of glucose production and glucose utilization in the nondiabetic subject. The prime factors affecting glucose turnover are the peripheral glucose and insulin concentrations. Following ingestion of a meal (or infusion of dextrose), the increase in plasma glucose level leads to an increase in plasma insulin. The elevation in plasma glucose concentration activates glycogen synthetase (the enzyme involved in glycogen synthesis) resulting in significant hepatic extraction of glucose, and suppresses both glycogenolysis and gluconeogenesis.[14–16] More insulin is secreted after oral ingestion of either dextrose or protein than after intravenous infusion due to the incretin effect.[17] Incretin is a substance(s) produced by the gastrointestinal tract which enhances insulin secretion. Insulin also decreases hepatic glucose production by inhibiting glycogenolysis and gluconeogenesis. The liver is very sensitive to small changes in insulin concentration. Under euglycemic conditions, an increase in the plasma insulin level from 10 μU/ml (typical preprandial insulin concentration) to 25 to 30 μU/ml results in a significant suppression of hepatic glucose production.[18] Near-maximal suppression occurs at an insulin concentration of 50 to 60 μU/ml (typical postprandial insulin concentration is 30-100 μU/ml).[18] Lack of suppression of endogenous hepatic glucose release in the presence of hyperinsulinemia thus denotes resistance to the action of insulin at the liver (hepatic insulin resistance). Glucose uptake is stimulated as the plasma glucose concentration increases because of the "mass action" of glucose.[19, 20] Significant stimulation of glucose utilization occurs at a plasma insulin concentration of 50 to 60 μU/mL.[18] Lack of appropriate glucose uptake in the presence of hyperinsulinemia denotes resistance to the action of insulin by extra-hepatic tissues (peripheral insulin resistance). Small increases in circulating insulin concentrations, therefore, have a proportionately greater effect on hepatic glucose production than on glucose utilization.

The combined hyperglycemia and hyperinsulinemia of the fed state convert the liver from an organ of glucose production to one of glucose uptake decreasing the amount of glucose that must be used by extrahepatic tissues. The concurrent augmentation of peripheral glucose utilization generally prevents the postprandial glucose concentration from exceeding 150 mg/dl. As the plasma glucose and insulin fall postprandially, the rates of glucose production and glucose utilization are restored to preprandial levels. The diminished insulin secretion allows hepatic glucose production to increase and limits glucose utilization in insulin sensitive tissues (liver, muscle, and fat).

The counter-regulatory, or counter-insulin hormones, (including glucagon, catecholamines, and cortisol) all increase hepatic glucose production. Each stimulates gluconeogenesis[21–23] and glycogenolysis[22–24] with cortisol also exerting a "permissive" effect. The term "permissive" is used in the sense that glucocorticoids are required for the full hepatic response to the other hormones. In addition, epinephrine is also capable of inhibiting insulin secretion,[25] and of decreasing insulin-induced suppression of hepatic glucose production.[26] As with glucose production, insulin and the counter-insulin hormones also have opposite effects on glucose utilization, with insulin increasing and the counter-insulin hormones decreasing glucose utilization. Glucagon inhibits hepatic glucose uptake,[27] while epinephrine and cortisol decrease peripheral use of glucose.[28, 29] Glucagon secretion does not fluctuate significantly throughout the day in a normal subject ingesting mixed meals. Similarly, normal feeding has little effect on the secretion of cortisol or catecholamines. Overfeeding with carbohydrate or fat calories, however, has been shown to lead to an elevation of sympathetic nervous system activity, as measured by tissue norepinephrine turnover.[30] These counter-regulatory hormones are key mediators of the metabolic response to injury.

ADMINISTRATION OF PARENTERAL DEXTROSE

Continuous intravenous feeding, as with TPN, differs from enteric feeding in several respects. First, nutrients immediately enter the systemic circulation bypassing initial entry through the splanchnic circulation and the insulinotropic effect of incretin(s). The peripheral insulin concentration in a nondiabetic subject receiving TPN is similar (60-90 μU/ml)[31, 32] to that of the fed state. Such chronic hyperinsulinemia is undesirable and may either cause or exacerbate insulin resistance, leading to further hyperinsulinemia.[33] Cyclic hyperalimentation, on the other hand, modifies the pattern in that the infusion is discontinued for a period each day.[32, 34] The peripheral insulin concentration has been shown to drop from 90 μU/ml (termination of TPN cycle) to 30 μU/ml (termination of infusion-free period),[32] a physiology which more closely approximates that of normal feeding. The drop in plasma glucose and insulin levels coupled with the rise in plasma glucagon concentration allows the

body to switch from a predominantly carbohydrate economy to a predominantly fat economy permitting endogenous fat reserves to provide energy fuels.

STRESS-INDUCED DIABETES MELLITUS

It is well recognized that, under conditions of severe medical or surgical stress, patients without an antecedent diagnosis of diabetes mellitus may become hyperglycemic.[35, 36] In a recent classification of diabetes mellitus proposed by the National Diabetes Data Group, "stress diabetes" is included under the category of secondary diabetes[37] and represents an important cause of hyperglycemia in the hospitalized patient. Severe stress is accompanied by a marked increase in the plasma concentration of glucagon, epinephrine, and cortisol.[35, 36, 38–41] Animal[42] and human studies[43, 44] have evaluated the role of counter-regulatory hormone actions and interactions in the pathogenesis of stress-induced hyperglycemia. The hormones were infused singly, and in combination, in healthy subjects in doses designed to reproduce the hormonal milieu of stress.[43] Single hormonal infusion caused only mild hyperglycemia (less than 120 mg/dl). Combined infusion, however, created a diabetic-like state with plasma glucose levels in excess of 200 mg/dl. Despite enhanced insulin secretion, the combined infusion produced a sustained hyperglycemia suggesting that a synergistic combination of counter-regulatory hormones is important in the pathogenesis of stress-induced diabetes mellitus. Interestingly, ketone regulation was not impaired; ketone body regulation is known to be maintained by small amounts of insulin.[45]

METABOLIC RESPONSE TO INJURY

The combined metabolic, immunologic, and hematologic response of a host to injury has been termed the acute-phase response. The response, designed both to limit the extent of injury and to promote healing, is in part mediated by monokines, including Interleukin-1 (IL-1) alpha and beta, and tumor-necrosis factor alpha/cachectin (TNF). IL-1, a family of polypeptides, is synthesized by activated cells, primarly monocytic and phagocytic cells lining the liver and spleen, in response to injury, inflammation, antigen, or toxin exposure. These peptides may act locally to promote T and B lymphocyte proliferation, or they may enter the circulation to regulate physiologic responses in distant tissues.[46–50] TNF, a monokine with distinct amino acid sequences and separate receptors from IL-1, is capable of inducing some of the same acute-phase changes as well as being uniquely able to mimic endotoxic shock. More recently, attention has focused on the effect of monokines on glucose metabolism.[51]

It is known that sepsis can be associated with either hyperglycemia or hypoglycemia, the latter a marker of poor prognosis. An elevation in the rate of glucose production has been reported in nonseptic burn patients and in bacteremic patients without complication.[52] By contrast, a depression in the rate of glucose production has been noted in septic patients with complications.[53] *In vitro* studies have documented an impairment of the gluconeogenic pathway during sepsis with depression in the activity of two enzymes, glucose-6-phosphatase[54–59] and phosphoenolpyruvate carboxykinase,[58, 60] the latter, a key rate-limiting step in the pathway which leads to glucose production from pyruvate or lactate. The mechanism by which injury can initiate common acute-phase changes with disparate effects on glucose metabolism has been clarified by the availability of recombinant cloning of monokines and the opportunity to study and separate the effects of each monokine. The impact of equivalent doses of recombinant human IL-1 beta and TNF on glucose kinetics in rats was examined.[51] IL-1 was previously shown to be capable of creating a stress hormonal profile;[61] this monokine has a dose-dependent effect on pancreatic islet cells, and at high doses, is toxic to islet cells.[62] Rates of both glucose appearance and utilization were increased in the IL-1 stimulated animals only. Also observed in this group was a rise in plasma glucose, a decrease in the ratio of insulin to glucagon, an increase in the percentage of glucose oxidized, and an increase in the metabolic clearance rate of glucose suggesting an enhanced utilization of glucose as a substrate. TNF administration failed to modify these parameters, although there was a tendency to induce insulin resistance. TNF is believed to be a direct or indirect mediator of the hypoglycemia characteristic of Gram-negative sepsis.

RATIONALE FOR DEXTROSE USE IN TPN

The beneficial aspects of infused glucose as a substrate in parenteral hyperalimentation are related to the provision of calories with a nitrogen-sparing effect. This effect stems from a suppression of hepatic glucose production (decreasing the need for gluconeogenic precursors) and from a stimulation of glucose oxidation (decreasing the requirement for amino acid oxidation as an energy source). To determine the "optimal" glucose infusion rate provided by TPN, glucose kinetics were studied in five postoperative, nonseptic patients receiving three glucose infusion rates (4, 7, and 9 mg/kg/min). After being maintained for 3 days on a glucose-free intravenous solution, the patients were given a dextrose and amino acid infusion. Glucose kinetics were studied in the basal state, and both 2 hr and 2 days after commencement of successive infusion rates to allow an assessment of adaptive changes to a given rate. The glucose concentration reached a steady-state level by 90 min of infusion with a mean value of 179,147, and 150 mg/dl (glucose infusion of 4, 7, and 9 mg/kg/min, respectively). A basal plasma insulin concentration of 7 μU/ml rose to 33 μU/ml after 2 hr of the lowest infusion rate with no further increase until the glucose infusion rate was increased to 9 mg/kg/min. This insulin concentration was significantly lower than that reported by previous investigators but was measured during a dextrose infusion only. The basal hepatic glucose production rate of 2.5 mg/kg/min was significantly suppressed during all infusion rates. Lack of a progressive rise in the plasma glucose level during the higher infusion rates was attributed to an enhanced ability of the tissues to clear

plasma glucose. This explains why, once adaptation to a glucose infusion rate occurs, as in TPN, the rate can be maintained or increased without leading to a marked elevation in plasma glucose concentration. The glucose clearance rate (rate of glucose uptake divided by the plasma glucose concentration used as an estimate of the ability of tissues to clear a given amount of glucose from the blood) rose from 2.5 to 6.6 mg/kg/min. The basal glucose oxidation rate of 0.6 mg/kg/min (26% of body glucose uptake) increased to 1.9 mg/kg/min (41% of total glucose uptake) during the 4 mg/kg/min infusion. There was not a direct relationship between the rate of glucose clearance and that of glucose oxidation; clearance continued to rise after oxidation had reached a plateau. The fate of nonoxidized glucose becomes critical. During the highest infusion rate, the ratio of carbon dioxide produced to oxygen consumed (respiratory quotient) was 1.1 suggesting that the net fate of some of the infused, nonoxidized glucose fraction was lipogenesis. In summary, during the 4 mg/kg/min infusion, hepatic glucose production was significantly suppressed and the percentage of glucose uptake oxidized was maximized. A glucose infusion in excess of 7 mg/kg/min did not provide added benefit as the body was incapable of oxidizing the additional glucose.

CARBOHYDRATE METABOLISM IN DIABETES MELLITUS

The homeostatic mechanisms which serve both to maintain euglycemia in the fasted state and to buffer the postprandial glycemic excursion are impaired in patients with diabetes mellitus. NIDDM is characterized by both preprandial and postprandial hyperglycemia. The preprandial hyperglycemia is attributed to an hepatic overproduction of glucose[64–67] resulting from insulin resistance[68–71] and from a lack of appropriate insulin secretion.[72] The mechanisms responsible for the postprandial hyperglycemia have more recently been studied.[73, 74] Prior to, and following mixed meal ingestion,[73] the rate of glucose appearance (glucose appearing in the systemic circulation) and the plasma glucose concentration were greater in the diabetic than nondiabetic group. The postprandial C-peptide response, a marker of endogenous insulin secretion, was lower in the diabetic patient in spite of a higher glucose concentration indicating an impairment in insulin secretion. The absolute rate of postprandial gluconeogenesis was greater in the diabetic than nondiabetic group. The pattern of hepatic glucose production was markedly different in the two groups. A prompt, sustained suppression of glucose release (nadir of 0.5 mg/kg/min) between 90 and 240 min postprandially was observed in the nondiabetic subjects. By contrast, in the diabetic patients, glucose release decreased slowly and progressively (nadir of 1.4 mg/kg/min) for 5 hr following the meal. The magnitude of postprandial suppression of glucose production (percent change from the preprandial rate) was equivalent. However, since the basal rate of glucose release was greater in the diabetic than nondiabetic group, the total amount of glucose released was greater in the diabetic patient. Postprandial hyperglycemia was exacerbated by lack of an appropriate increase in glucose uptake whether measured isotopically or by forearm glucose uptake. Thus, as has been proposed for fasting hyperglycemia, excessive hepatic glucose release and impaired glucose uptake are involved in the pathogenesis of postprandial hyperglycemia in patients with NIDDM.

In order to quantitate hepatic and extrahepatic insulin action at insulin concentrations commonly seen, hyperinsulinemic clamp studies were performed on noninsulin-dependent diabetic and nondiabetic subjects.[73] During an infusion of insulin, despite comparable plasma insulin concentrations (30 *vs* 34 μU/ml), and slightly higher glucose concentrations (116 *vs* 92 mg/dl), glucose production (1.3 *vs* 0.1 mg/kg/min) was greater and glucose utilization (1.9 *vs* 2.7 mg/kg/min) was less in the diabetic patients, indicating the presence of both hepatic and peripheral insulin resistance. Using turnover rates determined with [6-^{14}C] glucose as the standard, patients with IDDM also have been shown to exhibit hepatic and extrahepatic insulin resistance.[75]

Stress induces an even greater derangement in glucose metabolism in the diabetic patient than in the nondiabetic subject. A 5 hr infusion of stress dose counterregulatory hormones in young diabetic and nondiabetic subjects caused an exaggerated rise in plasma glucose in diabetic compared with nondiabetic subjects.[76] This occurred in spite of the fact that glucose kinetics had been normalized in both groups before the study by an insulin infusion. The augmented hyperglycemic response of the diabetic patients observed in this study helps explain why glycemic control often deteriorates in stressed diabetic patients.

ADMINISTRATION OF TPN: PRACTICAL CONSIDERATIONS

Indications for the initiation of nutritional support in the diabetic patient include, in addition to those of the nondiabetic subject, gastroparesis diabeticorum. The nutritional assessment and estimate of both energy and protein requirements are generally similar to those of the nondiabetic subject.[77–80] Stricter protein restriction, however, may be indicated in the patient with nephropathy in order to slow the decline in renal function, although this should not be an overriding consideration over the usual 3-week duration of acute care TPN.[81] Differentiation between IDDM and NIDDM can usually be established clinically. Insulin-dependent diabetes mellitus is characterized by an absolute requirement for insulin therapy, a tendency to ketosis, onset generally before age 30, and lack of obesity. Patients with noninsulin-dependent diabetes mellitus may not require insulin treatment, tend to be obese, and often acquire the disease after age 40.

Substrate Selection and Initiation of Insulin Therapy

As alluded to earlier, it is prudent to limit the daily dextrose infusion (including supplemental dextrose-containing solutions) to 400 g (4 mg/kg/min) in a 70-kg nondiabetic subject. The elevated basal hepatic glucose production rate coupled with the impaired extrahepatic glucose utilization of the diabetic, compared with the nondiabetic subject, warrants a more conservative ap-

proach to the initiation of dextrose. We have developed the following guidelines for TPN administration in the diabetic patient at the New England Deaconess Hospital. Dextrose in the initial TPN admixture is restricted to 100 to 150 g in patients with IDDM, NIDDM, and stress diabetes. The amount of insulin accompanying the initial dextrose infusion is based on the nonstressed prehospitalization requirements. A portion, usually 1/2, of the home daily insulin requirement is added to the TPN admixture as regular insulin. This conservative approach rarely results in an overestimation of insulin since it has been reported that approximately 50% of insulin present in the TPN admixture is metabolically inactive due to adherence to the infusion container and tubing.[82] Beef or pork insulin have traditionally been used, however, the recent availability and competitive pricing of biosynthetic human insulin has popularized its use. Human insulin is less immunogenic[83, 84] than animal insulin. Significant differences in potency, metabolic effects, and kinetic effects after intravenous administration have not yet been observed.[85, 86]

Acceptance of the trisubstrate mixture of dextrose, amino acid, and fat (3-in-1 mixture) as an effective form of nutritional support has led to its use in diabetic patients. Although not yet established, there is preliminary evidence in man that providing fat calories at high rates with TPN (above 50% of calories) may impair clearance by the reticuloendothelial system.[87] For this reason plus more extensive data in animals,[88] we limit parenteral fat to 30% of total calories which should be provided continuously as a 3-in-1 admixture. Provision of a portion of the calories as lipid permits a reduction in carbohydrate calories since a fat calorie is equally protein-sparing.[89] Lipid is calorically dense (9 kcal/g of fat) when compared to carbohydrate (3.4 kcal/g of hydrous dextrose) or to protein (4 kcal/g of protein). Equally important, the exogenous insulin requirement may decrease since lipid does not exert a substantial effect on insulin secretion.[90]

Optimization of Glycemic Control

After initiation of the insulin-containing TPN admixture with restricted dextrose calories, frequent (0700, 1500, and 2000) capillary glucose values are obtained in order to maintain glucose values between 100 and 200 mg/dl. Capillary glucose determinations are relatively inexpensive ($7.00) and offer quantitative information which is not provided by double-voided urine specimens. Subcutaneous administration of regular insulin is initiated based on the algorithm (Table I) which is different for the IDDM and NIDDM patient. A modification of this program may be necessary. Patients with a higher degree of insulin resistance (NIDDM, obese, and/or septic) may require more insulin. Conversely, some patients may need less insulin. This group might include patients with a lesser degree of insulin resistance (IDDM and/or lean), those receiving additional sources of insulin (via peritoneal dialysis or subcutaneous administration following initiation of enteral feeding), those with renal failure (decreased insulin clearance), or those in whom higher glucose values may be acceptable (ie, ischemic heart disease). The subcutaneously administered insulin required over a 24-hr period is totalled. Two-thirds of this amount is added to the TPN the following day to supplement the insulin already present, provided the capillary glucose levels have been less than 200 mg/dl. The total amount of supplemental insulin is added if the capillary glucose concentrations on the preceding day were greater than 200 mg/dl. When at least two of the three glucose values are less than 200 mg/dl, the dextrose load may be slowly advanced adjusting the TPN insulin to maintain the prior insulin to glucose ratio. The occurrence of severe hypoglycemia is uncommon in patients receiving TPN because of the continuous dextrose infusion. Immediate treatment of hypoglycemia includes dextrose supplementation either added directly or piggybacked to the TPN admixture. Subsequent hypoglycemia can be prevented by a significant (30–50%) reduction of insulin in the TPN. Adherence to this regimen prevents wide fluctuations in glucose concentration which are known to adversely affect leukocyte function.

TABLE I
Insulin algorithm: Suggested dose of subcutaneously administered regular insulin[a]

Capillary glucose (mg/dl)	IDDM (dose, units)	NIDDM (dose, units)	Stress diabetic (dose, units)
200–250	3	5	5
251–300	6	10	10
301–350	9	15	15
351–400	12	20	20

[a] For capillary glucose above 400 mg/dL, consult physician.

Bacterial function of polymorphonuclear leukocytes of the diabetic patient has been reported to be normal[91–95] or impaired.[96–101] The divergent conclusions may reflect use of different assays and an inadequate description of the patient's glycemic control, type of diabetes, and general health. Abnormalities in granulocyte adherence,[102, 103] chemotaxis,[95, 104, 105] phagocytosis,[97] and microbicidal function[99, 106] in poorly-controlled diabetics improve with more aggressive insulin therapy and improved glycemic control. Both intracellular defects[107] and the extracellular milieu (hyperglycemia and/or acidosis) contribute to the impaired function. These studies support the belief that optimal diabetic control is important to enhance leukocyte function. Hyperglycemia also adversely affects phagocytic function in nondiabetic subjects,[98] so glucose control in this group is equally important.

Conversely, hypoglycemia can also adversely affect the energy-dependent processes of chemotaxis and phagocytosis.[108] In the leukocyte, energy production occurs chiefly by the Embden-Meyerhof pathway in both nondiabetic and diabetic patients, but there is a greater contribution from the pentose shunt in diabetics.[109] The energy stores of the leukocyte are relatively small and an exogenous glucose supply is required for sustained energy activities.[110–111]

Monitoring

Careful monitoring of the diabetic patient receiving TPN is critical to successful use of this form of therapy.

Accurate recording of daily weights and fluid balance is essential. Close monitoring of serum electrolyte values becomes even more critical in the postoperative patient with multiple abdominal drains and significant nasogastric and ostomy losses. Insulin is capable of affecting sodium metabolism through an alteration of renal secretion of sodium, independent of changes in the glomerular filtration rate, renal blood flow, or the plasma concentrations of glucose or aldosterone.[112, 113] In the presence of a physiologic increase in the plasma insulin concentration, sodium excretion falls.[112, 113] This antinatriuretic effect of insulin can lead to edema; the marasmic IDDM patient may develop significant refeeding edema if the sodium in the TPN admixture is not initially restricted, (eg, sodium intake generally should not exceed sodium losses by more than 20 mEq/day).

Hyperinsulinemia may also cause a drop in plasma levels of potassium and phosphorus if the supplementation is insufficient. In addition to causing a flux of potassium into liver and muscle, a basal concentration of insulin is required for the maintenance of potassium homeostasis.[113] Tolerance to exogenous potassium supplementation may be limited, therefore, in the absence of basal insulin levels. The requirement for basal insulin becomes important in the patient with IDDM who is receiving cyclic hyperalimentation. Hyperkalemia, in the presence of hyperglycemia, is effectively treated by supplemental insulin. With the initiation of a dextrose infusion, the hyperinsulinemia can lead to an intracellular shift of phosphorus. The tendency to hypophosphatemia combined with the frequent use of phosphate-binding antacids in the postoperative or diabetic patient with nephropathy can result in significant phosphorus depletion. Even patients on dialysis can generally tolerate small amounts (5–10 mmol) of phosphorus in the TPN admixture every second or third day. Since sepsis may cause either hyperglycemia or hypoglycemia, a change in the plasma glucose concentration (provided there was no recent alteration in insulin supplementation, caloric provision, or medications known to affect carbohydrate metabolism) may be an early harbinger of infection.

Although no increase in subclavian vein thrombosis has been noted in diabetic patients receiving TPN,[114] alterations in the activity of antithrombin III (AT III), the principal inhibitor of the blood coagulation system, have been reported in diabetics. Despite normal plasma concentrations, decreased AT III biologic activity was detected in insulin-dependent diabetic patients,[115] in noninsulin dependent diabetic patients,[116] and in hyperglycemic nondiabetic subjects.[117] In patients with IDDM, the degree of reduction in antithrombin III activity was directly related to the level of both Hgb A_1C and the fasting plasma glucose concentration. The depression in activity of the inhibitor is at least partially caused by a nonenzymatic glycation of AT III, since *in vitro* glycation produced a significant decrease in thrombin-inhibiting action.[118] The addition of 6000 units of heparin to the TPN formula has been shown to reduce the incidence of clinically obvious central vein thrombosis from 5.4 to 1.2%[119] and 3000 units/liter shown to reduce clinically inapparent thrombosis to an even greater degree; 32% to 8%.[120]

SPECIAL CONSIDERATIONS

Preoperative Tapering of TPN

On the day before elective surgery, dextrose in the TPN is restricted to 150 g. At midnight, or approximately 6 hr before going to surgery, the TPN infusion is slowly tapered to prevent the development of glucoprivic symptoms. The rate of infusion is lowered to 40 cc per hr for approximately 60 min prior to discontinuation of the TPN and initiation of a dextrose-containing solution. If the infusion contains less than 100 g/liter of dextrose, tapering is unnecessary. On the morning of surgery, 1/2 of the usual dose of intermediate-duration insulin and the total amount of the usual dose of short-duration insulin is administered subcutaneously as intermediate-duration insulin. Close monitoring of plasma glucose and potassium levels is critical in the operative and perioperative period. Should emergent surgery be required, the infusion rate of the TPN may be rapidly tapered followed by initiation of an insulin-free infusion containing 100 g/l of dextrose. Data regarding the use of intraoperative TPN in diabetic patients is limited and generally not supportive of the practice. One of the studies measured plasma glucose concentrations in 20 patients, six diabetic, receiving intraoperative TPN.[121] The mean glucose level in the diabetic patient was 184 mg/dl preoperatively, 325 mg/dl (all > 250 mg/dl) 1-hr postoperatively, and 212 mg/dl 24 hr postoperatively. A second small series of 10 patients, one diabetic, reported that six of the 10 had plasma glucose concentrations in excess of 250 mg/dl.[122] On theoretic grounds, we prefer that no patient enter the operating room receiving insulin-containing TPN. Should intraoperative fluid resuscitation be required, an inadvertent increase in infusion rate of the TPN admixture (hypertonic dextrose, fixed dose of insulin, and electrolytes), rather than crystalloid, could lead to clinically important changes in serum glucose and potassium levels.

Transition to Enteral Nutrition

The ultimate goal of all patients receiving TPN is a transition to enteral nutrition. With the onset of enteral intake (orally or via a feeding tube), a small daily dose of subcutaneous intermediate-duration insulin is administered to cover the enteral calories. The possibility of erratic oral intake during the first few days and delayed nutrient absorption related to gastroparesis diabeticorum requires cautious use of intermediate-duration insulin and strict adherence to the insulin algorithm. As the glucose calories are decreased, the insulin is also lowered edec to maintain the same insulin to dextrose ratio in the TPN. Once the daily enteral caloric intake exceeds 1000 Kcal, subcutaneously administered intermediate-duration insulin should become the primary source of insulin therapy.

Peritoneal Dialysis and TPN

Peritoneal dialysis is an accepted alternative to hemodialysis in the management of patients with renal failure. In certain patients (postoperative, fluid-overloaded, or hypotensive) peritoneal dialysis may be better tolerated than hemodialysis. Glucose, the primary osmotic substrate used in the peritoneal dialysate to achieve fluid balance, is reliably absorbed from the peritoneal surface and may be a major source of calories if a high dextrose concentration is employed. It has been documented that up to 95% of administered glucose may be absorbed with peak absorption occurring over the first 30 min period.[123] This may lead to significant hyperglycemia in both diabetic and nondiabetic patients. Glycemic control can be optimized by the addition of insulin to the peritoneal dialysate.[124–126] Insulin administrered into the peritoneal cavity results in less hyperinsulinemia than if it is administered subcutaneously.[127] The amount of glucose absorbed can be estimated by measuring its concentration in the dialysis effluent and subtracting this value from the initial glucose dialysate concentration. A useful estimate is that the glucose concentration of the dialysis effluent is largely independent of the initial concentration and approximates 1000 mg/dl when blood glucose is under reasonable control. Therefore, when a 4.25% glucose dialysate is used, absorption of glucose approaches 35 g/liter. The balance of required energy and protein needs may be provided parenterally and if frequent exchanges with a high-dextrose concentration dialysate are used, only parenteral amino acid supplementation may be necessary.

Home Parenteral Nutrition

Although patients with severe gastroparesis diabeticorum can generally be fed at home by surgically or endoscopically placed jejunal tubes, occasionally, diabetic patients require home parenteral nutrition (HPN). Cyclic hyperalimentation, rather than a continuous infusion, is preferred because of convenience, lower plasma insulin levels, and less hepatobiliary complications. Hyperlimentation is started in the hospital, and once glycemic control is acceptable, nocturnal cycling is initiated without altering the insulin to dextrose ratio. The cycle is progressively shortened to a 10- to 12-hr period. The appropriateness of the TPN insulin dose can be judged by monitoring the fasting plasma glucose with the goal of maintaining this value below 200 mg/dl. However, we recognize that the ultimate acceptable value is a clinical compromise between safety and metabolic control. A subcutaneously administered basal component of intermediate (NPH or Lente, E.I. Lilly, Indianapolis, IN) or long (Utralente) duration insulin may be required by the patient to maintain glycemic control during the infusion-free period. Once-daily administration of Ultralente insulin, with its 40-hr half-life,[128] is an attractive option as it provides a relatively constant plasma insulin concentration.[129] In addition, the constant presence of basal insulin levels could help avoid potentially life-threatening hyperkalemia. The degree of home blood monitoring that is required must be individualized to each patient's situation. Finally, the increased propensity for infection that is characteristic of the diabetic patient necessitates meticulous outpatient follow-up by a multidisciplinary HPN team.

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