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Metabolic complications of parenteral nutrition in adults, part 1

IMAD F. BTAICHE AND NABIL KHALIDI

Purpose. Common metabolic complications associated with parenteral nutrition (PN) are reviewed, and the consequences of overfeeding and variables for patient monitoring are discussed.

Summary. Although PN is a lifesaving therapy in patients with gastrointestinal failure, its use may be associated with metabolic, infectious, and technical complications. The metabolic complications associated with PN in adult patients include hyperglycemia, hypoglycemia, hyperlipidemia, hypercapnia, refeeding syndrome, acid–base disturbances, liver complications, manganese toxicity, and metabolic bone disease. These complications may occur in the acute care or chronic care patient. The frequency and severity of these complications depend on patient- and PN-specific factors. Proper assessment of the patient's nutritional status; tailoring the macronutrient, micronutrient, fluid, and electrolyte requirements on the basis of the patient's underlying diseases, clinical status, and drug therapy; and monitoring the patient's tolerance of and response to nutritional support are essential in avoiding these complications. Early recognition of the signs and symptoms of complications and knowledge of the available pharmacologic and nonpharmacologic therapies are essential to proper management. PN should be used for the shortest period possible, and oral or enteral feeding should be initiated as soon as is clinically feasible. The gastrointestinal route remains the most physiologically appropriate and cost-effective way of providing nutritional support.

Conclusion. PN can lead to serious complications, many of which are associated with overfeeding. Close management is necessary to recognize and manage these complications.

Index terms: Electrolytes; Manganese; Minerals; Nutrition; Toxicity

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Parenteral nutrition (PN) therapy is the administration of nutritional support via the intravenous route when the gastrointestinal tract cannot or should not be used in patients who are malnourished or at risk for malnutrition.[1] Components of PN include macronutrients, or the energy-yielding substrates (amino acids, dextrose, lipids); micronutrients (vitamins, trace elements); fluids; and electrolytes. PN is a lifesaving therapy in patients with intestinal failure, but its use is not without complications. In a meta-analysis of studies that evaluated PN in critically ill patients, malnourished patients seemed to benefit most from PN and developed fewer complications than nonmalnourished patients who received PN.[2] Similarly, the Veterans Affairs Cooperative Study showed that perioperative PN increased complication rates in patients with low to moderate malnutrition but improved outcomes in certain high-risk, severely malnourished patients.[3] Any decision to use PN should be based on a risk–benefit analysis taking into consideration the associated complications and costs.

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This article reviews the common PN-associated metabolic complications, including hyperglycemia, hypoglycemia, hyperlipidemia, hypercapnia, refeeding syndrome, acid–base disturbances, liver complications, manganese toxicity, and metabolic bone disease. The consequences of overfeeding and patient-monitoring variables are also discussed.

Hyperglycemia

Dextrose in its hydrous form is the major energy source in PN and yields 3.4 kcal/g. It is also a source of carbon skeletons that are needed for tissue growth and repair. Dextrose tolerance is dependent on its rate of infusion and underlying patient conditions. The oxidation rate of dextrose is reduced in hypermetabolically stressed patients (e.g., critically ill patients and those with sepsis or organ failure), patients with diseases that alter insulin's effects (e.g., diabetes and acute pancreatitis),[4] elderly patients,[5] and patients receiving medications that alter glucose metabolism (e.g., corticosteroids, tacrolimus, and catecholamine vasopressors) (Table 1). Hyperglycemia is the most common complication associated with excessive dextrose infusion in PN. Uncontrolled hyperglycemia can cause fluid and electrolyte disturbances, hyperglycemic hyperosmolar nonketotic syndrome, and increased susceptibility to infection. Other complications of excessive dextrose infusion include hypertriglyceridemia, hepatic steatosis, and respiratory decompensation.

Table 1.
Factors Predisposing Patients to Hyperglycemia

Factor(s)	Mechanism(s)
Stress[a]	Increased counterregulatory hormones and cytokines, insulin resistance
Cirrhosis, uremia, obesity	Insulin resistance
Corticosteroid therapy	Enhanced glycogenolysis and gluconeogenesis, increased glucagon, insulin resistance
Catecholamine vasopressor therapy	Inhibition of glucose uptake, increased glycogenolysis, insulin resistance
Diabetes, pancreatitis, old age	Insulin insufficiency
Parenteral dextrose infusion	Bypass of liver first-pass effect, excessive dextrose infusion

[a]For example, sepsis, surgery, and organ failure.

Table 2.
Metabolic Response to Injury and Starvation[a]

Metabolic Variable	Response to Injury[b]	Response to Starvation[c]
Energy requirement	Increased	Decreased
Primary fuel	Mixed (RQ = 0.85)	Lipids (RQ = 0.75)
Insulin secretion	Increased (with insulin resistance)	Decreased
Serum ketones	Absent	Present
Release of counterregulatory hormones	Increased	Basal
Total body water	Increased	Decreased
Rate of proteolysis	Accelerated	Decreased
Rate of glycogenolysis	Accelerated	Increased
Rate of lipolysis	Increased	Increased
Body stores		
Skeletal muscle	Reduced	Reduced
Fat	Reduced	Reduced
Visceral proteins	Increased in liver and immune system	Preserved
Refeeding response	None (unless injury reversed)	Net anabolism
Loss of lean tissue	Accelerated	Gradual

[a]Adapted from reference 6, with permission. RQ = respiratory quotient.
[b]Typical setting: hospitalized patient or intensive-care-unit patient.
[c]Typical setting: patient with chronic disease (cardiac disease, chronic obstructive pulmonary disease, etc.).

Stress-induced hyperglycemia. Significant metabolic changes occur in response to injury or stress, leading to alterations in nutrient metabolism (Table 2).[6] In the absence of dextrose overfeeding, glucose intolerance in critically ill patients receiving PN is more a reflection of the severity of illness.[7] This is because stress during critical illness is associated with increased endogenous glucose production in response to increased release of counterregulatory hormones (e.g., catecholamines, cortisol, glucagon, and growth hormone) and cytokines (e.g., interleukin-1 and -6 and tumor necrosis factor-α). Counterregulatory hormones and cytokines are stress mediators that stimulate glycogenolysis and gluconeogenesis, causing the release of gluconeogenic precursors (e.g., glycerol, alanine, and lactate) from body tissues (Figures 1 and 2).

During stress, elevation of insulin levels in response to increased glucose production fails to suppress gluconeogenesis or to increase cellular glucose uptake.[8,9] The resultant insulin resistance, coupled with increased endogenous glucose production, results in hyperglycemia. Although dextrose infusion is expected to suppress gluconeogenesis, it fails to do so in stressed patients and instead worsens the hyperglycemia.[10] Critically ill patients, therefore, have lower tolerance of dextrose infusion than nonstressed subjects. Wolfe et al.[11] found that, in postoperative patients, dextrose infusion rates up to 7 mg/kg/min were well tolerated. However, the study was limited by a small sample (n = 5) and a relatively low stress level in the patients. In burn patients, who are more hypermetabolic, glucose oxidation was reported to reach a plateau at a dextrose infusion rate of 5 mg/kg/min.[12]

Figure 1. Simplified schematic of the mechanisms of stress-induced hyperglycemia. The main site of gluconeogenesis is the liver, with the kidneys playing a lesser role. Major substrates for gluconeogenesis are glycerol, alanine, and lactate. During stress, glucose synthesis from gluconeogenic precursors is increased as a result of increased release of counterregulatory hormones (catecholamines, glucagon, cortisol, growth hormone) and cytokines that oppose the restraining effects of insulin on gluconeogenesis and glycogenolysis. Glucagon stimulates glycogenolysis and hepatic gluconeogenesis. Epinephrine enhances skeletal muscle and hepatic glycogenolysis and stimulates kidney gluconeogenesis. Growth hormone stimulates gluconeogenesis and inhibits peripheral glucose uptake. Catecholamines and cortisol increase lipolysis. Cytokines (interleukin-1, interleukin-6, tumor necrosis factor-α) also contribute to increasing the glucose pool by enhancing glycogenolysis and gluconeogenesis, by inhibiting insulin release, and, indirectly, by increasing glucagon and cortisol synthesis. The end result of stress on glucose metabolism is increased endogenous glucose production and insulin resistance, which results in hyperglycemia.

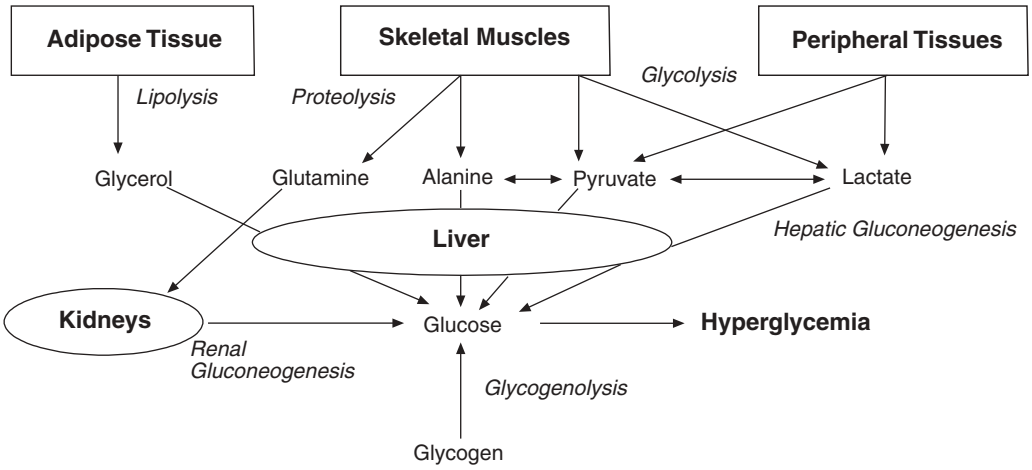
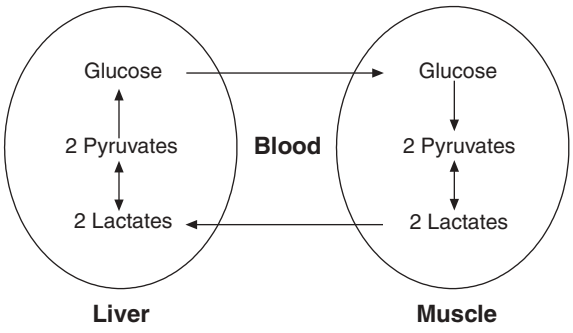


Figure 2. Cori cycle. Lactate, a byproduct of anaerobic glycolysis, is the most important gluconeogenic precursor. Most of the lactate is recycled by the liver to resynthesize glucose through the Cori cycle. The Cori cycle maintains glucose availability to vital tissues and prevents lactate accumulation.



However, lower dextrose infusion rates appear to be better tolerated in stressed patients. In a review of the cases of 102 adult nondiabetic patients receiving PN, 49% developed hyperglycemia with dextrose infusion rates of >5 mg/kg/min, compared with 11% when dextrose infusion rates were 4.1–5 mg/kg/min.[13] No cases of hyperglycemia were documented when the rate of dextrose infusion was maintained at ≤4 mg/kg/min. Therefore, a dextrose infusion rate of ≤4 mg/kg/min seems safe in the adult stressed patient.

Hyperglycemia and infection. Adequate nutrition is essential to maintaining a competent immune system[14] and hastening patient recovery.[15,16] However, dextrose overfeeding and the resultant hyperglycemia can be detrimental and may result in a depressed immune system and an increased risk of infection. Hyperglycemia impairs cellular and humoral host defenses by impairing neutrophil chemotaxis and adhesion, reducing phagocytosis, inhibiting complement fixation, and, possibly, enhancing microbial virulence.[17] In vitro data clearly demonstrated depressed phagocytic activity of polymorphonuclear granulocytes against gram-positive and gram-negative bacteria in a hypertonic dextrose milieu.[18] Animal data also showed impaired phagocytosis[19] and inhibition of immunoglobulin function[20] in a hyperglycemic state. In humans, the association between hyperglycemia and nosocomial and wound infections has been documented in postsurgical diabetic patients,[21,22] perioperative hyperglycemic diabetic patients,[23,24] and critically ill patients with suboptimal glucose control.[25] Also, diabetic patients with poor glycemic control have shown impaired polymorphonuclear leucocyte function[26,27] and reduced bactericidal ac-

tivity.[28] Although altered immune function in diabetics probably has multiple causes, phagocytic function improves with glucose control.[29]

Serum glucose concentrations. Hyperglycemia is loosely defined as serum glucose concentrations of >200 mg/dL.[30] Although serum glucose concentrations of 150–200 mg/dL have long been considered acceptable in stressed patients,[13,30-33] recent data suggest that tighter glucose control may improve patient outcomes. In a prospective randomized controlled study, Van Den Berghe et al.[25] evaluated the outcomes of intensive and conventional insulin therapy in 1548 adult surgical intensive care patients. The patients were randomized on admission to receive either intensive insulin therapy to maintain serum glucose concentrations between 80 and 110 mg/dL or conventional insulin therapy to maintain concentrations between 180 and 200 mg/dL if the serum glucose concentration was >215 mg/dL. Compared with conventional insulin therapy, intensive therapy significantly reduced mortality from 8% to 4.6% in all the patients during their stay in the intensive care unit ($p < 0.04$) and from 20.2% to 10.6% in patients who remained in the intensive care unit for more than five days ($p = 0.05$). Intensive insulin therapy was also associated with a 34% reduction in the rate of overall in-hospital mortality and a 46% reduction in the rate of septicemia, and it reduced the number of morbidity factors, such as acute renal failure, polyneuropathy, and ventilator dependency. Multivariate logistic regression analysis of the data by the same investigators showed that the benefits of intensive insulin therapy were the result of normoglycemia rather than the insulin dosage.[34]

Prevention and treatment. In the absence of dextrose overfeeding, a transient rise in serum glucose may still occur after the start of PN. Serum glucose concentrations usually normalize shortly thereafter, once endogenous insulin secretion adjusts to the rate of dextrose infusion. In stressed patients receiving PN, the maximum dextrose infusion rate should be kept at ≤4 mg/kg/min,[35] with dextrose providing 50–60% of total daily calories. Of the remaining calories, 20–30% are provided from lipid emulsions and 10–20% from proteins. In diabetic and critically ill patients requiring insulin, the dextrose infusion rate should be kept at 2 mg/kg/min until glucose control is achieved. Thereafter, the dextrose load can be slowly advanced to meet energy goals, and adjustments to the insulin dosage can be made as needed. A dextrose infusion rate of 2 mg/kg/min is usually sufficient to maximally suppress gluconeogenesis and prevent proteolysis.[36] In obese patients, the dextrose infusion rate should be based on the adjusted ideal body weight instead of the actual body weight. In case of hyperglycemia, a portion of the dextrose may be replaced by lipid calories, provided that hypertriglyceridemia is absent. Lipid emulsions should provide no more than 60% of the total daily calories.[37]

Insulin therapy is indicated if hyperglycemia persists despite all of the above measures. In the Van Den Berghe et al.[25] study, critically ill patients who received PN exclusively had a 26% higher insulin requirement to maintain normoglycemia than those who received a portion of their calories from enteral nutrition to provide identical amounts of daily calories.[34] One suggested option for treating hyperglycemia in PN patients is to start with sliding-scale subcutaneous regular insulin and then incorporate two thirds of the previous 24-hour subcutaneous insulin requirements in the PN solution.[38] The insulin dosage is thereafter adjusted in the PN solution on the basis of the additional subcutaneous insulin requirements. This practice may, however, leave patients hyperglycemic for prolonged periods, especially in the absence of concurrent treatment with intermediate-acting insulin. The low serum glucose target of 80–110 mg/dL proposed by Van Den Berghe and colleagues[25] necessitates the management of hyperglycemic critically ill patients with insulin drips instead of relying on a subcutaneous sliding-scale insulin regimen or the addition of regular insulin to the PN solution. Although adding insulin to the PN solution is convenient, it does not provide the flexibility of frequently adjusting the insulin dosage to achieve the targeted serum glucose level. Despite the intensive serum glucose monitoring required with a continuous infusion of regular insulin, it allows flexible adjustment of the insulin dosage and provides a safe and effective method of glucose control.[31,39]

Formerly, it was commonly accepted that moderate hyperglycemia during stress was beneficial, providing glucose to the brain and blood cells that depend solely on glucose for energy. A serum glucose concentration of 200 mg/dL is no longer considered an acceptable upper limit. However, a serum glucose threshold above which there is increased risk of morbidity and mortality has not been precisely determined, although a speculative upper limit of 145 mg/dL has been suggested.[40] Institutions may have begun to apply the intensive insulin regimen to critically ill patients because of the results of Van Den Berghe et al.,[25] but it is not yet clear how these results would apply to hospitalized and other critically ill nonsurgical hyperglycemic patients.[41]

Although exogenous insulin increases glucose clearance by promoting cellular glucose uptake, insulin does not increase glucose oxidation.[11,36] Little benefit is derived from infusing dextrose at rates that greatly exceed the body's glucose oxidative capacity when exogenous insulin becomes ineffective at increasing glucose uptake. In fact, excessive dex-

trose is converted to fat, leading to hypertriglyceridemia or fat deposits in the liver that may lead to hepatic steatosis.[42] Additionally, euglycemia may not necessarily rule out dextrose overfeeding, since the rate of glucose removal from the blood is not correlated with glucose oxidation. This may be seen during the early phases of overfeeding, especially in cachectic patients in whom a significant portion of dextrose is used to restore glycogen and fat stores.[12] To avoid overfeeding, energy expenditure is best measured with indirect calorimetry instead of relying on caloric estimates for critically ill patients.[43,44] Since energy expenditure varies from day to day, repeating energy-expenditure measurements about three times weekly in unstable critically ill patients would allow necessary adjustments to the patient's caloric intake while avoiding overfeeding.[45]

Hypoglycemia

Hypoglycemia is a less common complication of PN than hyperglycemia. Hypoglycemia usually occurs when PN is suddenly interrupted or as a result of an insulin overdose in the PN solution.[46] Reactive hypoglycemia occurs when elevated endogenous insulin levels do not adjust to the reduced dextrose infusion following PN cessation.[47] Although reactive hypoglycemia is not a universal occurrence,[48,49] some patients may be at higher risk because of underlying conditions that affect glucose regulation. These patients include those with chronic starvation, severe malnutrition, liver disease, and hypothyroidism.[50,51]

Hypoglycemia may result in significant morbidity if left untreated.[46,51] The key is prevention or early recognition. Reactive hypoglycemia can be prevented by gradually tapering PN over one to two hours before discontinuation, especially when adequate oral or enteral feeding is not provided.[47,52] Although there is no established period for its occurrence, reactive hypoglycemia may occur 15–60 minutes after PN is stopped. Monitoring serum glucose concentrations within that period is essential to promptly identifying and correcting hypoglycemia. Infusion of 10% dextrose injection immediately after discontinuing PN would prevent reactive hypoglycemia. If insulin is added to the PN solution, the insulin dosage should be regularly adjusted on the basis of blood glucose levels. Special attention should be given to reducing the insulin dosage when the underlying causes of hyperglycemia (e.g., acute pancreatitis, stress, and sepsis) have resolved, medications implicated in hyperglycemia (e.g., corticosteroids) are discontinued, or dextrose infusion is reduced or stopped.

Hyperlipidemia

Intravenous lipid emulsions cause changes in serum cholesterol and lipoprotein profiles, whereas either dextrose overfeeding[53] or lipid emulsions[54] can elevate serum triglyceride concentrations. Hyperlipidemia in patients receiving PN may lead to reduced pulmonary gas diffusion and pulmonary vascular resistance,[55] especially in patients with preexisting pulmonary vascular disease.[56-58] Severe hypertriglyceridemia may cause acute pancreatitis,[59,60] particularly when serum triglyceride concentrations exceed 1000 mg/dL.[61]

Predisposing factors. Hypertriglyceridemia associated with PN may be the result of excessive fatty acid synthesis from dextrose or of impaired lipid clearance. Other factors that affect lipid clearance also predispose patients to hypertriglyceridemia, such as sepsis, multiorgan failure,[62-64] obesity,[65] diabetes,[66] liver disease,[67] renal failure,[68,69] alcoholism,[70] a history of hyperlipidemia,[71] and pancreatitis.[72] Medications such as cyclosporine,[73] sirolimus,[74] and corticosteroids[75] also increase serum triglycerides by altering fat metabolism.

Hypertriglyceridemia may occur with the infusion of propofol. Propofol is formulated in a 10% lipid emulsion to improve its solubility. Similar to lipid emulsions, lipids in propofol can cause dose- and duration-dependent increases in serum triglyceride concentrations.[76] After a 10-day continuous i.v. infusion of propofol (infusion rate, 0.7–6.4 mg/kg/hr; cumulative dose, 66 g), serum triglyceride concentrations in critically ill patients increased to four times the normal values and remained elevated 72 hours after the therapy ended.[77] Because hypertriglyceridemia was observed with lower than usual lipid doses given in PN, it was speculated that propofol could also have direct effects on reducing fat metabolism independent of its lipid effect.[78]

Hypertriglyceridemia and dextrose. Dextrose overfeeding is the main cause of hypertriglyceridemia in patients receiving PN. Normally, 1 g of glucose yields about 0.35 g of fat during net whole-body lipogenesis. Lipogenesis occurs in the liver and adipose tissue through the action of the fatty acid synthetase and acetyl–coenzyme A synthetase enzymes that convert dextrose into fatty acids. Formed fatty acids are then transported from the liver as triglyceride-rich very-low-density lipoproteins (VLDLs).[79-81] When hypertriglyceridemia develops during PN, dextrose overfeeding should be ruled out first and the dextrose load reduced if necessary. Reducing the amount of lipids may be necessary if hypertriglyceridemia does not improve with reduction of the dextrose load.

Hyperlipidemia and lipid emulsions. Intravenous lipid emulsions are used in PN as a source of calories and essential fatty acids (linoleic acid, linolenic acid). Lipid emulsions currently marketed in the United States are mainly composed of long-chain triglycerides (LCTs) derived from soybean oil or a 50:50 mixture by weight of soybean oil and safflow-

er oil. Lipid emulsions are available as 10%, 20%, and 30% oil-in-water emulsions that yield 1.1, 2, and 3 kcal/mL, respectively. Lipid emulsion particles are similar in structure and size to the naturally occurring chylomicrons, except for the lack of apoproteins (polypeptides that activate enzyme systems) on their external coating. Once in the bloodstream, lipid particles acquire apoproteins that promote their hydrolysis by lipoprotein lipase (LPL) to release fatty acids. Formed fatty acids circulate in the bloodstream as free fatty acids or bound to albumin. Free fatty acids either undergo oxidation to generate energy or be stored as triglycerides in adipose tissue. The remnants are metabolized in the liver by the liver lipase enzyme to make VLDLs and low-density lipoproteins (LDLs). In healthy individuals, the elimination half-life of lipid emulsions is around 30 minutes, with about 80% of lipids cleared in one hour. However, lipid clearance is reduced in stressed patients as a result of decreased LPL activity, which may lead to lipid accumulation.

Although there is a resemblance in the composition of different lipid emulsions, a major difference is the phospholipid-to-triglyceride (PL:TG) ratio that plays a role in the clearance differences among various emulsions. The PL:TG ratio of the 10%, 20%, and 30% lipid emulsions is 0.12, 0.06, and 0.04, respectively. This translates to two times more phospholipids in the 10% lipid emulsion than in the 20% emulsion and three times more phospholipids in the 10% emulsion than in the 30% emulsion. Large phospholipid amounts have been proposed to cause the appearance of the abnormal lipoprotein X in the blood of patients who receive the 10% emulsion.[82,83] In a comparison of the 10% and 20% lipid emulsions, plasma lipoprotein X concentrations were shown to be directly correlated with the lipoprotein amounts in the lipid formulation.[84] Formation of lipoprotein X with the 10% lipid infusion was reported in adult patients[85] and pediatric patients.[86] After infusion of the 10% lipid emulsion, excess phospholipids form single-bilayer vesicles that extract cholesterol from tissues and produce lipoprotein X. Lipoprotein X particles are rich in phospholipids (60%) and cholesterol (25%) and contain small amounts of triglycerides. They appear in the bloodstream shortly after the infusion of the 10% lipid emulsion and have a long half-life (two to four days).[84,87] The role of lipoprotein X in hypertriglyceridemia is believed to result from its competition with lipid particles for clearance by LPL.[88]

Studies have compared the effects of different lipid emulsions on plasma lipid profiles and the formation of lipoprotein X.[85,89] In adult surgical patients, the 10% lipid emulsion caused marked increases in phospholipids, cholesterol, and LDLs.[85] However, serum triglycerides, VLDLs, and high-density lipoproteins remained normal. When the 10% lipid emulsion was replaced by the 20% emulsion at equal lipid doses, there was a rapid decline in serum triglyceride, cholesterol, and phospholipid concentrations.[89] Even at higher lipid doses, the 20% emulsion resulted in lower serum triglyceride levels than the 10% emulsion.[90] In postoperative trauma patients receiving PN, a five-day infusion of the 10% emulsion caused a progressive increase in plasma phospholipids and cholesterol levels.[91] These effects were not observed with the 20% emulsion, while serum triglycerides and free fatty acids remained constant and similar in each group. In another study that compared the 10% and 30% lipid emulsions in critically ill patients, lower median plasma triglyceride, phospholipid, and cholesterol concentrations were seen with the 30% emulsion, along with the formation of lipoprotein X with the 10% but not the 30% emulsion.[92]

Studies comparing the 20% and 30% lipid emulsions showed that both formulations are well tolerated. Although serum triglyceride and fatty acid concentrations increase with the infusion of either emulsion, serum phospholipid concentrations were higher after the 20% emulsion was infused than after administration of the 30% emulsion.[93] In critically ill patients with trauma and sepsis, higher total serum cholesterol and triglyceride concentrations were seen with the 20% than the 30% lipid emulsion. However, neither emulsion caused the formation of lipoprotein X.[94] The long-term consequences of lipoprotein X remain unknown, but no harmful effects have been observed during short-term infusion of the 10% lipid emulsion.

Medium-chain triglycerides. Newer parenteral lipid formulations of mixed medium-chain triglycerides (MCTs) and LCTs are available in Europe in 75:25 or 50:50 MCT:LCT ratios. The 75:25 formulation is expected to be marketed in the United States soon. Current LCT emulsions supply fatty acids with 16 and 18 carbons, whereas MCTs comprise fatty acids with 8- to 10-carbon chains. The inclusion of LCTs in MCT–LCT mixtures is crucial to providing the essential fatty acids and linoleic and linolenic acids (18 carbons each) that are not supplied in formulations with MCTs alone.

MCTs have the advantage of being oxidized faster than LCTs. This may allow MCTs to be used in patients with reduced lipid clearance, since they may result in fewer serum lipid abnormalities and lower serum triglyceride concentrations.[95,96] Although some studies have found that MCT–LCT emulsions may result in a better lipid profile and an improved nitrogen balance compared with LCT lipid emulsions,[97,98] these differences have not been observed in other studies.[99] In one study of critically ill surgical patients who received PN,

administration of the 50:50 MCT:LCT formulation or an LCT lipid emulsion resulted in no significant differences in energy expenditure, nitrogen balance, or levels of prealbumin, albumin, cholesterol, triglycerides, and free fatty acids.[100]

MCT–LCT formulations have also been studied in patients with renal failure. Druml et al.[101] examined the elimination and hydrolysis of MCT–LCT emulsions in seven patients with acute renal failure and six healthy control subjects. In the control subjects, the clearance of MCTs was slightly higher than that of LCTs, but the rise in serum triglyceride levels was similar. The reduction in clearance of both LCTs and MCTs was similar in the renal failure group and the control subjects, as was the increase in serum triglycerides. The authors concluded that lipid clearance is reduced in acute renal failure, regardless of whether an MCT or LCT lipid emulsion is used.

In septic patients with respiratory failure, LCT administration was associated with more significant changes in pulmonary function than infusion of the 50:50 MCT:LCT emulsion.[102] However, a study in patients with acute respiratory distress syndrome found no differences in pulmonary hemodynamics, arterial oxygen tension, or mixed venous partial pressure of oxygen after infusion of MCT–LCT or LCT lipid emulsions.[103] The mixed results obtained with the MCT–LCT formulations may be partly related to different study designs and small study groups. More research is needed before routine use of mixed MCT–LCT formulations can be recommended.

Management and monitoring. Serum triglycerides should be regularly monitored during PN therapy. If hypertriglyceridemia occurs, reducing the dextrose or lipid dosage is necessary, depending on the cause. When hypertriglyceridemia coincides with dextrose overfeeding, the first step is to reduce the dextrose load and treat the hyperglycemia. Since the LPL activity is capacity limited, reducing the lipid dosage and infusing lipids continuously would enhance lipid clearance. Continuous lipid infusion over 24 hours improves lipid oxidation[104] and results in better plasma fatty acid profiles[105] than cyclic lipid infusion. Also, since parenteral fat may, in theory, be immunosuppressive by reducing phagocytosis and cytokine secretion,[106] continuous lipid infusion may impose a smaller burden on the reticuloendothelial system.[107] The clinical effects of lipid emulsions on immune function remain controversial and require further study.[108] Normally, the lipid infusion rate can be maintained at around 0.12 g/kg/hr, but lower rates may be better tolerated in critically ill patients or patients with impaired lipid clearance.[109] In most cases, lipid emulsions provide about one third of the total daily calories contained in PN.[110]

In patients treated with propofol, calories from propofol formulations should be counted as lipid calories equivalent to 1.1 kcal/mL. The lipid dosage should be adjusted to avoid hypertriglyceridemia.[111] A new propofol vehicle of MCT–LCT emulsion is available in Europe but not the United States. Early studies of this product showed that serum triglyceride concentrations did not significantly differ from those observed with propofol mixed with LCTs, but faster triglyceride clearance occurred with the MCT–LCT emulsion containing propofol.[112] An investigational 2% (20-mg/mL) propofol formulation that provides fewer lipids than the 1% (10-mg/mL) formulation has resulted in lower serum triglyceride concentrations.[113] The MCT–LCT and 2% propofol formulations may provide an alternative to the 1% propofol formulation currently marketed in the United States. At this point, serum triglycerides should be monitored during propofol infusion, and, if hypertriglyceridemia occurs, propofol should be discontinued and another sedative agent, such as lorazepam or midazolam, should be used.

Monitoring serum phospholipids, fatty acids, cholesterol, and lipoprotein X levels is not a routine practice. Usually, baseline serum triglyceride concentrations are measured before PN initiation and once the lipid goal is reached. Thereafter, the frequency of serum triglyceride measurements depends on the severity of hypertriglyceridemia. Daily lipid infusion should be withheld when the serum is lipemic or when serum triglyceride concentrations exceed 400 mg/dL. In such cases, the lipid emulsion dose should be given only two or three times weekly. To prevent essential fatty acid deficiency, linoleic acid should provide approximately 3–5% of total caloric intake. Providing 300 mL of the 20% lipid emulsion twice weekly is sufficient to prevent essential fatty acid deficiency in adult patients. Since no lipoprotein X was detected after infusion of the 20% or 30% lipid emulsion, these two formulations seem to be better alternatives than the 10% emulsion. Although some studies found that the 30% lipid emulsion resulted in a more favorable lipid profile than the 20% emulsion, especially in stressed patients,[94] the 20% emulsion appears to be equally well tolerated.[114] The 30% lipid emulsion appears to be most advantageous in patients with fluid restriction because of its higher caloric concentration. The 30% emulsion, however, has FDA-approved labeling for infusion in total nutrient admixtures (TNAs), whereas the 10% and 20% emulsions can be administered with PN solutions by infusion through a secondary i.v. line or mixed in a TNA. Despite the promise of MCT-based lipid emulsions, clinical data on their superiority to LCT emulsions have been equivocal. As such, parenteral MCT–LCT emulsions cannot be advocated for general use until suffi-

cient data demonstrate their metabolic superiority to LCTs. Also, the projected high cost of MCT–LCT emulsions would add another financial burden to patient care.

Hypercapnia

Hypercapnia is defined as excess retention of carbon dioxide. Overfeeding of total calories and dextrose causes hypercapnia due to excess carbon dioxide production (VCO_2) relative to oxygen consumption (VO_2) during carbohydrate metabolism. This relationship is described by the respiratory quotient ($RQ = VCO_2/VO_2$). The RQ for fat, protein, and carbohydrates is 0.7, 0.8, and 1, respectively. An RQ of >1 indicates excessive calorie and carbohydrate intake and net fat synthesis.[12,115] When excess carbon dioxide is produced, compensatory mechanisms are stimulated to increase minute ventilation in order to eliminate the excess carbon dioxide.[116] The resultant increase in respiratory workload may cause acute respiratory acidosis and precipitate respiratory insufficiency that may necessitate mechanical ventilation.[117,118] These effects may occur within hours of dextrose overfeeding in severely malnourished patients[119] and in patients with limited pulmonary reserve, such as those with chronic obstructive pulmonary disease.[120] High dextrose loads may also prolong ventilator dependence in mechanically ventilated patients[117,121] and cause respiratory insufficiency in elderly and frail patients who have depleted protein and energy stores.[122]

Overfeeding with dextrose and total calories can increase the RQ. In a review of critically ill patients who received PN, 73% of patients who had an RQ of >1 received dextrose infusion rates of >4 mg/kg/min.[123] In a study of stable mechanically ventilated patients who were receiving PN, high calories instead of a high percentage of dextrose intake increased CO_2 production. VCO_2 did not significantly change with isocaloric PN regimens, despite a change in the dextrose:lipids ratio that varied from 40% to 75% of carbohydrates and 40% to 5% of lipids, with protein intake fixed at 20% of total calories. However, a significant increase in VCO_2 occurred when total calories were increased from one to two times the estimated resting energy expenditure, with the proportion of dextrose, lipid, and protein calories fixed at 60%, 20%, and 20%, respectively.[124] Energy-mixed substrates from fat, carbohydrates, and protein are better utilized than a fat-free regimen and yield an RQ of ~0.85. Lipid emulsions appear to have a more sustained effect on balancing the RQ when they are infused continuously over 24 hours rather than intermittently over 12 hours.[104]

Although the RQ may be a tool for assessing optimal caloric delivery, it may be insensitive to overfeeding in hypermetabolic patients.[125,126] Overfeeding causes only minor changes in the RQ in the hypermetabolic patient, because oxygen consumption and minute ventilation increase when carbon dioxide production increases.[127] Thus, the RQ is a more sensitive and reliable indicator of overfeeding in patients who are not hypermetabolic.[121]

The refeeding syndrome

The refeeding syndrome describes the fluid and electrolyte imbalances, glucose intolerance, and vitamin deficiencies that occur in severely malnourished individuals during rapid nutritional repletion.[128,129] The metabolic and physiological disturbances of the refeeding syndrome may be significant and can result in cardiac, pulmonary, renal, gastrointestinal, and neuromuscular complications and even death.[130] This syndrome may occur with oral, enteral, or parenteral feeding. Conditions that predispose patients to the refeeding syndrome include chronic starvation, prolonged fasting, chronic alcoholism, anorexia nervosa, malabsorption syndromes, morbid obesity followed by significant weight loss, and wasting diseases, such as cancer and AIDS.[128,131] Table 2 summarizes characteristics of the metabolic response to starvation.[6]

Electrolyte disturbances. Electrolyte abnormalities that may occur with the refeeding syndrome include sodium retention, hypophosphatemia, hypokalemia, and hypomagnesemia. Sodium is the major extracellular cation, and its serum concentration dictates the extracellular fluid volume. Sodium retention usually occurs in the early phase of the refeeding syndrome and is exacerbated by excessive sodium and fluid intake. This may lead to fluid overload, pulmonary edema,[132] and cardiac decompensation[133] that may be detrimental to cachectic patients whose cardiac mass and function are reduced by severe malnutrition.[133,134]

In contrast to sodium, potassium and magnesium are primarily intracellular ions. Potassium is the major intracellular cation, and phosphorus is the major intracellular anion. The intracellular distribution of these electrolytes makes it difficult to assess body stores by their measured serum concentrations. While their serum concentrations may appear normal, their body stores can in fact be depleted by starvation.[135] There is a state of energy preservation and hypoinsulinemia during starvation; it is rapidly reversed when carbohydrate feeding is initiated. Carbohydrates stimulate insulin secretion, which in turn causes phosphorus and potassium to shift intracellularly. The combined effects of increased demands and intracellular flux of these electrolytes lead to severe extracellular electrolyte deficiency. Severe deficiencies of phosphorus, potassium, and magnesium can cause significant morbidity and mortality if left untreated.[129]

The clinical features of electrolyte disturbances depend on the severity of the electrolyte deficiency. Phosphorus regulates carbohydrate, pro-

tein, and fat metabolism; plays a role in glycolysis; and is required for the formation of phosphorylated compounds, including adenosine triphosphate, 2,3-diphosphoglycerate, and glycerol-3-phosphate dehydrogenase. These high-energy phosphate compounds are increasingly needed during glycolysis, especially when glucose is the major source of energy. The increased demand for phosphates is, however, opposed by reduced availability of phosphorylated compounds in phosphate deficiency.[136-138] Severe hypophosphatemia can cause respiratory, neuromuscular, and hematologic complications. Paresthesia, weakness, and convulsions were reported in severely malnourished patients with hypophosphatemia within four to seven days of PN initiation.[139] Respiratory failure, acute cardiopulmonary decompensation, and death from severe hypophosphatemia occurred soon after PN initiation in cachectic patients with anorexia nervosa and malabsorption syndrome.[135]

Hypokalemia and hypomagnesemia can coexist, and their signs and symptoms can be similar.[140] Severe hypokalemia can cause cardiac, neuromuscular, gastrointestinal, metabolic, and renal dysfunction. Similarly, hypomagnesemia can have cardiac, neuromuscular, and gastrointestinal effects. Successful correction of hypokalemia cannot be achieved without correcting the magnesium deficiency. Hypomagnesemia may cause hyperaldosteronism that increases renal potassium excretion or may affect cellular potassium distribution. Simultaneous supplementation of potassium and magnesium in documented cases of deficiencies is essential for rapid and successful correction of the deficiencies.

Thiamine deficiency. Since thiamine is a water-soluble vitamin, its body stores can be easily depleted by malnutrition and weight loss. Dextrose infusion places additional demand on thiamine, since thiamine is a cofactor in intermediate carbohydrate metabolism. Wernicke's encephalopathy due to thiamine deficiency has been reported in malnourished individuals[141,142] and in thiamine-deficient patients who received high carbohydrate loads.[143] Thiamine is a coenzyme for glucose metabolism and is essential for the conversion of pyruvate and the oxidation of ketoacids. With thiamine deficiency, pyruvate is converted to lactate instead of being oxidized via the citric acid cycle.[144] Excessive lactate formation has resulted in cases of lactic acidosis and death in patients who received PN without thiamine supplementation.[145-148]

Prevention and treatment. Patients at risk of the refeeding syndrome should be identified early to prevent the associated complications. Nutrient delivery should be instituted gradually and advanced slowly to achieve the caloric goal over three to five days. Empirical supplementation of phosphorus, potassium, and magnesium can be started before feeding is begun. Thereafter, electrolytes are supplemented during feeding, with amounts based on serum electrolyte concentrations. Although most reports have focused on thiamine deficiency, other vitamins may also be deficient in the malnourished patient. However, the importance of other vitamin deficiencies in the refeeding syndrome is less clear. Adding parenteral multivitamins to PN solutions provides daily requirements consistent with the recommendations of the American Medical Association.[149] Marketed adult parenteral multivitamins provide 3 or 6 mg of thiamine per vial added to the daily PN. However, since thiamine requirements are increased in cachectic patients, additional daily supplementation of thiamine at 100 mg/day has been suggested for patients at risk of deficiency.[129] Supplementation of other vitamins, especially folic acid, at 1 mg/day may also be necessary.

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