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Management of Hyperglycemia During Enteral and Parenteral Nutrition Therapy

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Abstract

Hyperglycemia is a frequent complication of enteral and parenteral nutrition in hospitalized patients. Extensive evidence from observational studies indicates that the development of hyperglycemia during parenteral and enteral nutrition is associated with an increased risk of death and infectious complications. There are no specific guidelines recommending glycemic targets and effective strategies for the management of hyperglycemia during specialized nutritional support. Managing hyperglycemia in these patients should include optimization of carbohydrate content and administration of intravenous or subcutaneous insulin therapy. The administration of continuous insulin infusion and insulin addition to nutrition bag are efficient approaches to control hyperglycemia during parenteral nutrition. Subcutaneous administration of long-acting insulin with scheduled or corrective doses of short-acting insulin is superior to the sliding scale insulin strategy in patients receiving enteral feedings. Randomized controlled studies are needed to evaluate safe and effective therapeutic strategies for the management of hyperglycemia in patients receiving nutritional support.

Keywords

Nutrition support; Insulin; Diabetes mellitus; Parenteral nutrition; Enteral nutrition; Hyperglycemia

Introduction

Hyperglycemia is prevalent in hospitalized patients [1••]. In urban community hospitals, hyperglycemia defined as either fasting blood glucose of more than 126 mg/dL or random blood glucose above 200 mg/dL was observed in 32–38 % of patients with and without diabetes history [2, 3]. Up to 20 % to 30 % of patients admitted to hospitals in the United States will have a known diagnosis of diabetes mellitus [3, 4]. The prevalence of hyperglycemia in patients receiving a specialized nutritional support is higher, and reported in up to 30 % of patients receiving enteral nutrition and more than half of patients receiving parenteral nutrition [5–8].

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The pathogenesis of hyperglycemia during nutrition support is complex. Elevation of blood glucose occurs as the result of increased hepatic glucose production and reduced glucose utilization by peripheral tissues during the stress of hospitalization [9–12]. Acute illness, surgery, and trauma raise levels of stress mediators, namely stress hormones and cytokines, that interfere with carbohydrate metabolism leading to hyperglycemia [11, 13, 14]. Peripheral insulin resistance during stress and illness is common and is associated with down-regulation of intracellular signaling through the insulin receptor. Bed rest by itself was recently demonstrated to diminish glucose uptake and insulin signaling by insulin-dependent tissues [15, 16]. Insulin resistance increases by 7- to 8-fold in patients undergoing surgical procedures largely explained by increases in glucagon, cortisol, and catecholamines [17]. Finally, excessive delivery of glucose and gluconeogenic substrates via enteral or parenteral rout in hospitalized patients also contributes to hyperglycemia [18, 19].

Patients with hyperglycemia are at higher risk of complications and mortality [1••]. Several prospective observational and randomized control trials have demonstrated that managing hyperglycemia reduces rates of infections and mortality in surgical patients with diabetes [20–22]. It is clear that hyperglycemia is a frequent complication of enteral and parenteral nutrition in both patients with and without diabetes [23, 24, 25••, 26•], and that the development of hyperglycemia during nutrition support increases the risk of complications and mortality [27]. Despite the benefits of glucose control in improving clinical outcome, glucose control continues to be deficient and physicians frequently delay or fail to start insulin treatment in patients receiving nutrition support. The management of hyperglycemia during nutrition support is also complicated by the presence of accompanying comorbidities and by the limited number of well-designed clinical trials targeting the treatment of hyperglycemia during nutrition support. In this review, we discuss the results of available studies on the treatment of hyperglycemia during enteral and parenteral nutrition.

Glycemic Goals in Patients Receiving Enteral and Parenteral Nutrition

A consensus statement from the American Association of Clinical Endocrinologists and American Diabetes Association (AACE/ADA) recommends a target blood glucose (BG) level between 140 to 180 mg/dL in critically ill patients [28]. In the majority of non-critically ill patients, the pre-meal BG target should be between 100 and 140 mg/ dL and random BG below 180 mg/dL, provided that these targets could be safely achieved. Higher BG ranges are recommended for patients prone to hypoglycemia and/or with severe comorbidities, while more stringent glycemic targets are recommended in patients with stable glucose trends [28]. Despite the lack of prospective randomized control trials in support of intensive glycemic control in patients receiving specialized nutrition support, several observational and intervention studies in intensive care unit (ICU) patients have suggested that a BG goal less than 150 mg/dL improves clinical outcomes in patients receiving nutrition support [29, 30•].

The association between the development of hyperglycemia during total parenteral nutrition (TPN) and poor clinical hospital outcome is well established (Table 1). Patients with hyperglycemia during TPN are more likely to be admitted to the ICU, have longer hospital and higher mortality rates, and require a more prolonged course of PN compared with subjects without hyperglycemia [23, 31]. The relationship between adverse outcomes and hyperglycemia appears to be continuous across different patient cohorts with BG levels starting at more than 114 mg/dL [23, 27, 31, 32]. In 1 study, each 10 mg/dL increase in mean BG above a reference value of 114 mg/dL was associated with a 7–9 % increase in the risk of infection and organ dysfunction [32]. Other studies have demonstrated that the development of hyperglycemia in patients receiving TPN increased mortality and hospital complications including systemic infections and renal failure (Table 1).

The evidence is conflicting whether diabetes status confers an additional risk for complications in patients receiving nutrition support. In 1 study, having a known history of diabetes increased risk of death, cardiac complications, and systemic infections compared with patients without a history of diabetes [32]. Others studies, however, reported that a history of diabetes does not increase the risk of complications or mortality [23, 31], and may even have a protective effect on mortality despite higher levels of BG [23]. An analysis of pooled dataset from 2 prospective randomized controlled trials (RCTs) with a high proportion of the patients receiving TPN reported no effects of established diabetes on hyperglycemia-associated adverse outcomes in the ICU [29, 33].

Managing Hyperglycemia in Patients During Specialized Nutrition Support

Nutrition guidelines state that any patient who is unable to consume adequate nutrients orally (≥60 % nutrition needs) for at least 5 days in the ICU, or 7 to 14 days in the general ward, should be a candidate for specialized nutrition support [34]. The metabolic needs of most hospitalized subjects can be supported by providing no more than 25–35 calories/kg/d depending on degree of illness [35, 36] while some malnourished critically ill patients may require only 15–25 calories/kg/d [37]. With regards to carbohydrate content, this will translate into a diet containing ~200 g/d carbohydrates [36]. Both enteral and parenteral nutrition have been proven effective in preventing the adverse effects of starvation and malnutrition in hospitalized patients. However, enteral nutrition is preferred to parenteral nutrition in clinical practice [34] for multiple reasons, including higher rates of hyperglycemia and infections with TPN use [26•, 38–40]. Strategies for managing hyperglycemia to appropriate glycemic goals in patients requiring specialized nutrition support should consider modifications in content of feedings as well as initiation of safe and effective pharmacological therapies to reduce blood glucose levels. Unfortunately, clinical inertia, fear of hypoglycemia, poor communication among teams involved in patient care, and complexity of patient care frequently precludes the implementation of these pathways.

Managing Hyperglycemia in Patients During Enteral Nutrition

Few prospective randomized studies have addressed effective strategies to prevent or correct hyperglycemia in patients receiving enteral nutrition support. Specific strategies to control hyperglycemia during enteral nutrition therapy should include the assessment of caloric needs and composition of nutrition support formulas and the use of pharmacologic agents available in clinical practice.

The Effects of Enteral Formula Macronutrient Composition on Hyperglycemia

—Enteral nutrition is started via nasogastric tube or, less frequently, percutaneous gastric tube. Standard enteral formulas contain 1–2 cal/ml and, in general, consist of protein, lipid in the form of long-chain triglycerides, and carbohydrates. In contrast to the standard formulas in which carbohydrates provide 55–60 % of total calories, new diabetic specific formulas have replaced parts of carbohydrates with monounsaturated fatty acids (up to 35 % of total calories), dietary fiber (10–15 g/L), and fructose [41, 42]. Short-term and long-term studies in non-acutely ill patients with diabetes, the use of lower carbohydrate content in enteral formulas has been shown to reduce hyperglycemia, improve hemoglobin A1c, and lower insulin requirements compared with the standard high carbohydrate formulas [43–50]. However, there are no RCT in critically ill patients with diabetes investigating whether the use of diabetic specific formulas [51] will improve inpatient glycemic control compared with the treatment with standard enteral nutrition formulas.

The use of enteral nutrition support may be associated with several complications that may impact the care of hospitalized patients. Enteral nutrition may cause bacterial colonization of the stomach, high gastric residual volumes with subsequent risk of aspiration pneumonia,

and diarrhea. In addition, unanticipated dislodgement of feeding tubes or temporary discontinuation of nutrition due to nausea, or for diagnostic testing may result in increased risk of hypoglycemic events in patients treated with insulin or with oral hypoglycemic agents [25••, 52].

Pharmacological Therapy of Hyperglycemia During Enteral Nutrition—Only 1 prospective RCT evaluated the effectiveness of different insulin regimens in managing hyperglycemia in hospitalized patients receiving enteral nutrition support [25••]. In this study, 50 patients with and without a history of diabetes and BG levels above 140 mg/dL were randomized to receive either a standard therapy consisting of sliding scale regular insulin (SSRI) or a long-acting insulin glargine administered once daily. Though at the end of the study there was no difference in glycemic control between the groups, 48 % of patients in the SSRI group required rescue therapy with intermediate-acting insulin NPH due to persistent hyperglycemia. An average total daily insulin dose during enteral nutrition therapy was 27 units or 0.33 units/ kg [25••]. There was a difference in insulin dosage between diabetic and nondiabetic patients. Patients with diabetes required a total daily dose of 0.61 ±0.28 units/kg and those with no history of diabetes received 0.39 ± 0.28 units/kg per day. The results of this investigation suggest that starting long-acting insulin glargine along with correctional short-acting insulin is an effective strategy to manage hyperglycemia during enteral nutrition. Several retrospective studies have also reported on insulin administration dosage in diabetic and nondiabetic patients during enteral nutrition in the hospital. In 1 study, insulin glargine at an average daily dose of 34 units was sufficient to control hyperglycemia in patients on enteral nutrition containing 200 g of carbohydrates per day [53]. Two other studies compared glycemic outcomes with use of intermediate-acting insulin NPH [54] or biphasic insulin 70/30 [55]. Insulin NPH administered every 6 hours was more effective and safer than SSRI or NPH injected every 4 hours in patients with diabetic and nondiabetic hyperglycemia [54]. In another study, 70/30-biphasic insulin given trice daily was superior to its twice daily administration, or insulin glargine/lispro combination [55]. The rates of hypoglycemia in these studies varied between 0.9 % and 1.4 % [25••, 54, 55], which is considered to be safe for hospitalized patients receiving insulin therapy [1••]. In the absence of head-to-head trials comparing NPH and basal insulin analogs (glargine or detemir), it is not known if the insulin analogs offer any additional benefit in improving glycemic control or in reducing hypoglycemic events. On the one hand, the use of NPH may be preferable because of the shorter half-life that facilitates its titration or discontinuation in the event tube feedings are stopped and lower cost. On the other hand, basal insulins have been proven safe and effective in the management of inpatient hyperglycemia in medicine and surgery patients. In a study in patients with type 1 diabetes, the use of insulin analogs resulted in less hypoglycemia compared with the use of NPH and regular insulin [56]. Low dose basal insulin in combination with supplemental regular insulin was shown to be effective in providing glycemic control in majority of patients receiving enteral feedings [25••].

Managing Hyperglycemia in Patients During Parenteral Nutrition

The use of total parenteral nutrition (TPN) has been shown to improve nutritional status and lower hospital complications in the critically ill patients [26•, 39, 57, 58]. Specialized nutrition support is now recognized as a cost-effective way for hospitals to improve clinical outcomes in patients with critical illness, severe burns, prolonged ileus, after transplantation, trauma, abdominal surgery, pancreatitis, and long-term ventilation [26•]. However, excessive glucose administration during TPN may have metabolic disadvantages manifested by accelerated lipogenesis in the liver and fat tissue [59], increase thermogenesis [60], and a higher oxidation of the glucose to CO2 resulting in an increased work of breathing [61]. In addition, TPN has been associated with gut mucosal atrophy, overfeeding, hyperglycemia,

an increased risk of infectious complications, and increased mortality in critically ill patients [26•]. The development of hyperglycemia during TPN in the hospital has been independently associated with higher rates of mortality and hospital complications [23, 27, 31, 32]. These observations indicate that prevention and correction of hyperglycemia via either modification of nutrient composition or by insulin infusion should be strongly considered during TPN therapy.

The Effects of TPN Macronutrient Composition Modifications on Hyperglycemia—Total caloric target range for most adults in the ICU is 20– 25 kcal/kg [26•]. As recommended by several professional societies and experts in the field, the macronutrient composition of parenteral nutrition should consist of at least 2 g/kg/ d of glucose (the only carbohydrate in PN formulations), 0.7–1.5 g/kg/d of lipid emulsions, and 1.3–1.5 g/kg/d of amino acids calculated per ideal body weight [26•, 37, 62, 63]. A significant body of evidence indicates that dextrose administration rate in TPN above 4 mg/kg/min is a significant predictor of hyperglycemia in nondiabetic critically ill patients. In retrospective and prospective studies, a glucose infusion rate of more than 4 mg/kg/min was associated with higher rates of hyperglycemia and insulin use in ICU [6, 13, 64]. One approach to reduce the development of hyperglycemia during TPN therapy is to lower the amount of infused dextrose to 150 g/d, a glucose load that is sufficient in meeting metabolic demands of the brain and basic cellular functions [37]. Recently, 1 study suggested that a lower glucose load in TPN was associated with improved mortality in ICU [65]. In 88 nondiabetic patients admitted to ICU, dextrose infusion rate of 1.8 ± 1.3 g/kg/d was associated with less hyperglycemia, lower rate of insulin use, and lower mortality rates compared with patients receiving dextrose infusion rates of 2.6 ± 1.4 g/kg/d [65]. Although it may be reasonable to limit dextrose load in TPN to 150–200 g/d as one of the measures to prevent the development of hyperglycemia during TPN use, prospective randomized studies are needed to determine if the differences in glucose load reduces the risk of hyperglycemia and improves clinical outcome in critically ill patients.

The timing of parenteral nutrition initiation in critically ill patients should also be considered as a potential strategy in reducing the risk of complications associated with TPN. A recent large multicenter European study [66••] compared early initiation of nutrition support with intravenous dextrose (20 % solution) on ICU day 1 and enteral plus parenteral nutrition on day 2 with late initiation of nutrition support using intravenous dextrose (5 % solution) on day 1, enteral nutrition on day 2, and parenteral nutrition on day 8. Withholding parenteral nutrition until day 8 resulted in significantly less ICU infections, shorter course of organ dysfunction, shorter ICU stay, and reduced health care costs. Importantly, BG levels were the same in both groups averaging 102–107 mg/dL but the amount of insulin infused was significantly lower in a group assigned to the late initiation of parenteral nutrition support. Another study reported that the addition of enteral nutrition to TPN to compensate for ~30 % of nutritional requirements significantly lowered interstitial glucose concentrations and reduced insulin resistance compared with patients in whom nutrition was delivered via TPN only [67].

The increased rate of TPN-associated complications may also be related to the type of lipid solutions used in TPN solutions. The only FDA-approved lipid emulsion is a soybean oil-based lipid emulsion with high content of linoleic acid and ω-6 polyunsaturated fatty acids (PUFA) [12]. Due to its high content of linoleic acid, soybean based lipid emulsions might promote the generation of arachidonic acid-derived eicosanoids and exaggerate the inflammatory response during stress and trauma [68, 69]. Infusion of ω-6 PUFA can exert immunosuppressive effects and impair endothelial function, nitric oxide production, and autonomic nervous system activity [68, 70]. The concern about the potential complications associated with the use of ω-6 PUFA has led to the development of alternative lipid

emulsions for parenteral nutrition. Lipid emulsions with lower linoleic acid content by partly replacing soybean oil with olive oil (ClinOleic; Baxter, Chicago, IL, USA) have improved the safety of TPN [71, 72]. Our group has systematically evaluated whether olive oil-based parenteral nutrition is different from the standard soybean oil-based admixture. In a recent prospective, randomized, cross-over study we compared the vascular, metabolic, immune and inflammatory effects of a 24-hour infusion of soybean oil-based PN, olive oil-based PN, lipid free PN, and normal saline in healthy subjects [73]. Soybean oil-based PN increased blood pressure and reduced brachial artery flow mediated dilatation from baseline by 23 % at 4 hours and by 25 % at 24 hours, both $P<0.01$; in contrast, olive oil-PN, and lipid free-PN did not change either blood pressure or endothelial function compared with normal saline infusion in these individuals subjects [73]. In a second study, we compared clinical outcomes in 100 medical-surgical ICU patients receiving TPN containing standard soybean oil-based lipid emulsion vs TPN containing olive oil-based lipid emulsion [74••]. We observed similar rates of infectious and noninfectious complications and no significant differences in hospital or ICU or hospital stay, glycemic control, and inflammatory and oxidative stress markers in medical and surgical ICU patients [74••].

Several reports have suggested that supplementation of parenteral nutrition with glutamine and chromium may improve glycemic control and clinical outcomes in critically ill patients receiving TPN. Glutamine is an abundant muscle-free amino acid, which was shown to attenuate high fat-induced hyperglycemia and insulin resistance [75]. Recently, a prospective, double-blind, randomized trial demonstrated that supplementing TPN with alanine-glutamine dipeptide reduces the amount of insulin required to manage hyperglycemia by 54 % compared with use of standard TPN [76]. Addition of chromium to TPN was suggested as one of the options in managing extreme insulin resistance [63].

Insulin Therapy During Total Parenteral Nutrition—Insulin is the treatment of choice to control hyperglycemia during TPN. Both subcutaneous and intravenous insulin have been shown to be effective in managing hyperglycemia in these patients [13, 77]. In critically ill or hemodynamically compromised patients, treatment with intravenous continuous insulin infusion is preferred as it allows frequent dose adjustments to control glucose values [78]. Some studies have reported that the use of separate insulin infusion is more cost effective than adding insulin in the TPN bag. However, other studies have shown that adding insulin to TPN mixture is clinically safe and effective in controlling hyperglycemia during TPN. Adding insulin at the ratio of 1 unit of insulin per 11 g of dextrose in patients with diabetes receiving TPN containing 150–300 g of carbohydrates per day is an effective initial step to prevent and reduce hyperglycemia [79]. In another institution, a rate of 1 unit of regular insulin per 10 g of dextrose is used at the commencement of TPN infusion in diabetic patients followed by daily titration of insulin by 0.5 unit per 10 g of dextrose if blood glucose target is not achieved [77]. In another study, glycemic goals during TPN use in diabetic subjects were achieved by insulin to carbohydrate ratio of 1:4 [19].

There are only few studies that have addressed hyperglycemia management during TPN in nondiabetic patients. Initiation of insulin at the rate of 1 unit per 20 g of dextrose with further up titration to 1:15 ratio if blood glucose was above 140 mg/dL was reported as an effective tool in managing nondiabetic hyperglycemia in the ICU [80]. On average, hyperglycemia in patients without established diabetes was managed by an insulin to carbohydrate ratio of 1:15 or average total daily insulin dose of 0.3 ± 0.2 U/kg/d [80].

Hypoglycemia in Patients Receiving Specialized Nutrition Support

The development of hypoglycemia in critically ill patients has been shown to be associated with increased risk of complications, length of hospital stay, and mortality. In addition, fear of hypoglycemia in hospitalized patients remains a major barrier in achieving optimal glycemic control in the inpatient setting [1••]. Patients who receive enteral or parenteral nutrition are at higher risk for hypoglycemia as clinical manifestations of declining blood glucose levels are blunted in the patients. Hypoglycemia can develop due to excess of insulin dose, abrupt discontinuation of nutrition support, recovery from acute illness, decreases in dose of glucocorticosteroids or vasopressors, and progressive organ failure. Strategies that would prevent and address hypoglycemia in patients during specialized nutrition support involve approaches that are pertinent to the management of inpatient hypoglycemia in general as well as would reflect specifics of this patient population (Table 2).

Conclusions

Hyperglycemia is common in hospitalized patients receiving specialized nutritional support. The development of hyperglycemia during parenteral and enteral nutrition is independently associated with adverse clinical outcome and mortality. There are only few small prospective trials that addressed glycemic targets and outcomes in this patient population. Pending results of large, randomized, controlled studies, we recommend following current guidelines from professional societies on glycemic goals in managing hyperglycemia in hospitalized patients [1••, 28, 37, 62, 81]. Our approach to the management of hyperglycemia in the hospitalized patient receiving specialized nutrition support is provided in Fig. 1. We recommend that capillary glucose monitoring be initiated for patients with or without a history of diabetes receiving enteral and parenteral nutrition. Glucose monitoring can be discontinued in patients without a prior history of diabetes if BG values are less than 140 mg/dL without insulin therapy for 24–48 hours following achievement of desired caloric intake. In patients with history of diabetes, insulin therapy should be initiated for BG more than 140 mg/dL. For those patients without a history of diabetes, insulin therapy is indicated if blood glucose is above 180 mg/dL or in patients with persistent requirement for correction insulin. Providers may also consider reduction in carbohydrate content in order to lower blood glucose concentration. Frequent reassessment of patients' clinical status is critical not only to allow maintaining adequate glycemic control but also to prevent hypoglycemia. Future studies are needed to determine safe and beneficial glycemic targets in patients receiving enteral and parenteral nutrition as well as to determine optimal glycemic control strategies.

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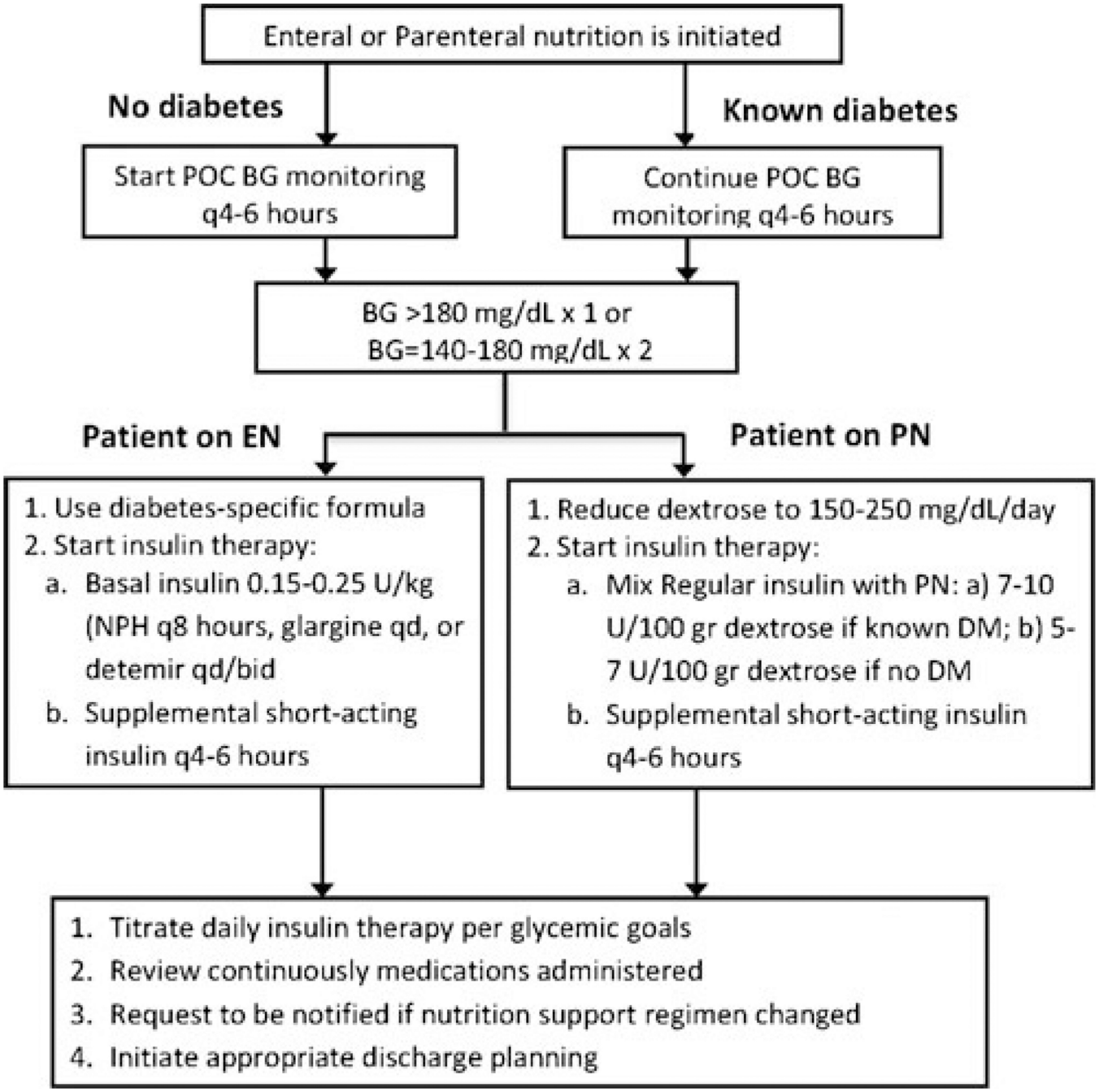

Fig. 1.
Approach to the management of hyperglycemia in patients receiving enteral or parenteral nutrition. POC—point of care; BG— blood glucose; EN—enteral nutrition; PN—parenteral nutrition; DM— diabetes mellitus

Table 1

Adverse outcomes significantly associated with hyperglycemia after adjustment for multiple factors in patients receiving TPN

	N	BG level, mg/dL	Odds ratio (95 % CI), $P<0.05$		
			Death	Any infection	Renal failure
Cheung et al. [23]	111	<125 vs >164	10.9 (2.0–60.5)	3.9 (1.2–12.0)	10.9 (1.2–98.1)
Lin et al. [32]	457	<114 vs 137–180	2.3 (1.2–4.5)	2.7 (1.5–4.9)	NS
Pasquel et al. [27]	276	≤ 120 vs >180	2.8 (1.2–6.8)	3.6* (1.6–8.4)	2.2 (1.02–4.81)
Sarkisian et al. [31]	100	≤ 180 vs >180	7.22 (1.1–48.3)	NS	NS

*Data reported for pneumonia only

BG blood glucose; NS nonsignificant

Table 2

Preventing and managing hypoglycemia in patients receiving enteral and parenteral nutrition

1 Prevention of hypoglycemia:

- If tube feeding is interrupted:
  - Start intravenous 10 % dextrose infusion 50 mL/h,
  - Consider reducing next dose of long- or intermediate-acting insulin, and
  - Increase frequency of bedside glucose monitoring
- If parenteral nutrition is interrupted:
  - Consider reducing next dose of long- or intermediate-acting insulin (if used)
- Reduce dose of scheduled insulin if:
  - Renal insufficiency
  - Discontinuation or reduction in steroids
  - Discontinuation of vasopressors
  - Decrease in carbohydrate intake

2 Management of hypoglycemia (BG<70 mg/dL):

- Administer intravenously Dextrose 50 % 25–50 mL
  - If repeat BG is <70 in 15 minutes, repeat dextrose intravenous push and start intravenous 10 % Dextrose infusion 50 mL/h
  - If repeat BG is ≥70 in 15 min, measure BG in 1 hour, and repeat treatment until BG is >100 mg/dL
- Administer intramuscular 1 mg Glucagon if there is no intravenous access present
- Reduce or hold next dose of long- or intermediate-acting insulin (if used)