Published in final edited form as:

Curr Gastroenterol Rep. 2011 August ; 13(4): 388–394. doi:10.1007/s11894-011-0204-x.

Carbohydrate Provision in the Era of Tight Glucose Control

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Abstract

Glycemic control in the critically ill patient has remained a controversial issue over the last decade. Several large trials, with widely varying results, have generated significant interest in defining the optimal target for blood-glucose control necessary for improving care while minimizing morbidity. Nutritional support has evolved into an additional area of critical care where appropriate practices have been associated with improved patient outcomes. Carbohydrate provision can impact blood-glucose levels, and the relationship between nutrition and glucose levels has become more complex in the era of improved glycemic control. This review discusses the controversy surrounding intensive-insulin therapy in the intensive care unit and explores the relationship with nutritional support, both in the enteral and parenteral form. Achieving realistic goals in both carbohydrate provision and glycemic control may improve patient outcome, and are not mutually exclusive practices.

Keywords

Glycemic Control; Glucose Control; Intensive Insulin Therapy; Enteral Nutrition; Parenteral Nutrition; Carbohydrate Provision

Introduction

Few issues in critical care medicine have generated as much debate in recent years as the topic of glycemic control in the intensive care unit (ICU). The issue was critically re-examined following the landmark study by Van den Berghe et al.[1] in 2001 describing the effect of tight glucose control (80 – 110 mg/dL) on outcome in a predominately perioperative cardiac patient population. Their study demonstrated a significant

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Disclosure:

No potential conflicts of interest relevant to this article were reported.

improvement in mortality compared to the control group. The authors repeated this study in a medical ICU. And while the study fell short of re-demonstrating the efficacy of this practice in the entire population, tight glucose control appeared to benefit patients remaining in the ICU for longer periods of time [2]. However, over the next several years, multiple studies demonstrated the potentially harmful ramifications of tight glucose control when applied to different critical care units, or by different investigators. Many questions remain unresolved with regard to the appropriate utilization of this information in clinical practice. On the other hand, nutritional support in the ICU has the potential to improve patient outcome, being associated with decreased infectious complications, length of stay, and possibly mortality. The administration of nutritional products containing varying levels of carbohydrates can impact glucose levels as well. Following the initiation of intensive insulin protocols, carbohydrate provision in critically ill patients became a more important, yet rarely examined contributor to glucose management. The focus of this review is to assimilate recent literature concerning these two interesting and controversial aspects of care of the critically ill patient. We suggest that achieving realistic goals in both carbohydrate provision, whether enterally or parenterally, and glycemic control may improve patient outcome, and are not contradictory practices.

Glycemic Control: The Emergence of a New Paradigm

Chronic hyperglycemia from diabetes has long been known to have serious clinical consequences [3]. The concept that hyperglycemia in the acute setting could result in increasing morbidity and mortality in critically ill patients was a less established concept prior to 2001. Van den Berghe et al. [1] conducted a prospective, randomized controlled trial (RCT) which demonstrated patients randomized to an intensive insulin regimen, maintaining blood-glucose concentrations between 80 – 110 mg/dL, had significantly reduced bloodstream infections, acute renal failure, red-cell transfusions, critical illness polyneuropathy, days of mechanical ventilation, and overall mortality, when compared to a control group [1]. As a result, acute hyperglycemia in the setting of critical illness became an increasingly discussed and investigated issue.

The mechanisms responsible for these observations have yet to be fully elucidated. The hyperglycemia associated with diabetes has been characterized as prothrombotic, Proinflammatory, and highly destructive to the microvascular environment in the chronic setting. A review of the literature by Turina et al. [4] explored the relationship between acute hyperglycemia and the innate immune system. Increased circulating levels of inflammatory cytokines such as IL-6 and tumor necrosis factor α (TNF- α) have been observed in diabetic patients [5]. Advanced glycosylation end products (AGEs) as a result of chronic hyperglycemia may have a role in the generation of reactive-oxygen species (ROS), altering the balance in favor of oxidative stress at the endothelial level [6]. Again, the role of AGEs in the acute setting, if any, is less defined. Acute hyperglycemia may impair chemotaxis, leukocyte adhesion and transmigration, complement activation, and several other components of the innate immune system to varying degrees [4].

Much of the hyperglycemia frequently observed in the critically ill patient is thought to be a byproduct of insulin resistance in addition to, or as a part of, the classically described hormonal stress response. Mowery et al. [7] suggest that much of the increased morbidity and mortality recently attributed to morbid obesity in the setting of trauma is more closely associated with insulin resistance than obesity itself, and insulin resistance is an independent predictor of mortality. A recent study examined insulin resistance in skeletal muscle tissue following acute trauma and hemorrhage in a rat model. The mechanism of insulin resistance in this study appeared to be at the insulin receptor level, involving decreased tyrosine phosphorylation of the insulin receptor, and absent insulin-induced protein kinase B (Akt)

phosphorylation. Interestingly, insulin resistance and resultant hyperglycemia were noted to occur as early as 60 minutes following acute hemorrhage. Insulin receptor defects were apparent to a much greater degree in peripheral skeletal muscle when compared to diaphragmatic muscle. Defects in insulin signaling were absent in cardiac muscle tissue [8]. To this end, admission glucose values, due in part to increasing peripheral insulin resistance in the acute setting, may have predictive value with regard to outcome in certain patient populations, and may serve as a marker of the insult magnitude [9]. The exogenous provision of insulin may minimize the consequences of this response and act in a therapeutic, antiinflammatory fashion. In an LPS-induced systemic inflammation model in pigs, exogenously administered insulin to target normoglycemia resulted in decreased circulating levels of TNF- α [10]. Albacker et al. [11] measured circulating cytokine levels in patients undergoing cardiopulmonary bypass, and demonstrated that a group receiving 20% dextrose solution in conjunction with intravenous insulin infusion to maintain blood glucose between 70 – 110 mg/dL had significantly decreased levels of IL-6, IL-8, and TNF- α when compared to a group targeted at less than 180 mg/dL.

Several studies conducted by Arabi et al., Brunkhorst et al., De La Rosa et al., and Preiser et al. followed the Leuven study [12–15]. These investigators were unable to reproduce Van den Berghe's results, and were associated with alarmingly higher rates of hypoglycemia. In smaller RCTs, some morbidity benefit was seen with tight glucose control protocols [16 – 19]. Given the discrepancy between the Leuven study and other RCTs, the Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial was designed, to 90% power, to validate the findings of the Leuven study. The control group had blood glucose levels of 140–180 mg/dL, which was lower than the control group in the Leuven study. The NICE-SUGAR trial showed that patients with tighter glycemic control had increased 90-day mortality when compared to controls, further questioning the utility and safety of tight glycemic control protocols in the ICU [20••].

Hypoglycemia is the most obvious and dreaded complication of intensive insulin therapy (IIT) and may contribute to some of the differences observed in the trials. In the NICE-SUGAR trial, severe hypoglycemia was documented in 6.8% of patients undergoing intensive glucose control, while only 0.5% of patients in the conventional group had documented episodes of hypoglycemia [20••]. This was a much higher incidence than was present in the Leuven trials. Obligate glucose consumers include the central nervous system, and hypoglycemic coma is a severe consequence of profound hypoglycemia. However, there may be more subtle clinical consequences of hypoglycemia in the absence of overt neurologic decompensation that may be hard to detect in sedated, critically ill patients. And so the true impact of hypoglycemia in this patient population is difficult to estimate. Three potential explanations for the association between hypoglycemia and mortality have been cited. First, the severity of hypoglycemia may simply be associated with severity of illness [21]. Second, hypoglycemia may in and of itself be a biomarker of death [22]. Third, hypoglycemia may have a directly toxic effect by increasing systemic inflammation, inhibiting the corticosteroid response to stress, increasing cerebral vasodilation, or other unidentified mechanisms [22 – 25].

Glycemic variability is an emerging concept that many believe may also play a role. Glycemic variability, as the term suggests, refers to the degree to which blood glucose values fluctuate in an individual patient over the course of time. Variability in glucose levels has been shown to be an independent predictor of mortality [26,27•]. Possible explanations for this finding are similar to those given for characterizing hypoglycemia. Less glycemic variability may simply reflect more attention to detail at the level of medical and nursing care. Less variability could be associated with less severe disease and a less disturbed host response [26]. As both hypoglycemia and increased glucose variability are thought to be

independent predictors of mortality, both should be assessed in the ICU setting, but the relative importance of each variable remains to be determined.

A decade after the initial study, debate continues with regard to the appropriate goals of glucose control. The post hoc analysis of the two Leuven studies and the NICE-SUGAR trial showed that an intermediate range (140 – 180 mg/dL) of targeted glycemic control may be preferable as morbidity appeared similar, and hypoglycemic episodes were minimized [28]. In addition, a recent meta-analysis conducted by Marik and Preiser [29••] of seven trials revealed a significant association between an increasing number of parenterally provided calories in conjunction with IIT and decreasing 28-day mortality. It appears that patients that may most benefit from IIT are those who receive substantial parenteral support, and that, in fact, may be the real key to the differences observed between the major trials.

Understanding the Limitations of Available Data

Patient population

Explanations for the variability observed in the results of the multiple trials are many. One notable difference between trials involves the heterogeneity of the patient populations that have been investigated. Three of the more publicized trials varied tremendously in this regard, as Leuven 1 involved “surgical ICU” patients, but 70% of their population consisted of postoperative elective cardiac and thoracic surgery patients receiving hypertonic-glucose solutions via parenteral nutrition (PN) for dietary support. Leuven 2 was conducted in the medical ICU, and the NICE-SUGAR trial consisted of a heterogeneous population consisting of both medical and surgical patients [1, 2, 20••].

As an example, glycemic aberrations are the norm in sepsis, another common indication for ICU admission, as hyperglycemia has been observed in 50% to 90% of septic patients, with increasing rates depending upon the severity of illness. Severe hypoglycemia, as defined by a serum glucose <40 mg/dL in one study, was observed in 2% of patients with sepsis and 12% of patients with septic shock, even with the liberalization of targeted glucose levels to 140 mg/dL [30]. Patients with septic shock are clearly at increased risk for hypoglycemia during IIT, even when compared to patients carrying the same diagnosis, but of differing disease severity. Krinsley [31] makes the point that two large multicenter RTCs examining IIT in septic patients (Glucontrol and VISEP) were closed early due to the high incidence of hypoglycemia, and that these results were predictable considering the patient population on which they focused.

Defining the variables

As differences in patient populations may have contributed to the observed variability in these large studies, so too may the discrepancies in defining many of the key variables being compared played a role. Before an in-depth analysis of any data set is meaningful, one must first define the involved variables and ensure the uniformity of the manner by which they are collected. This has remained a difficult task with regard to the literature surrounding both the advantages and disadvantages of tight glucose control. For example, a recent study conducted a review of 49 articles published concerning glucose and insulin utilization in the ICU. The authors noted 15 different glucose values being categorized as “hypoglycemia” and these values ranged from <40 – <72 mg/dL [32]. Indeed, this wide range can dramatically affect the results from any paper interpreted, and can also influence meta-analyses attempting to compile information. The same is true regarding the manner in which glucose values are obtained. Bedside glucometers rely on capillary blood obtained from peripheral fingersticks. Only 56% of fingerstick glucometer analyses correlated with central laboratory analysis in one study, and this already unreliable value dropped to 26% correlation in periods of hypoglycemia [33]. When trying to delineate the difference

between targeting 110 mg/dL or 140 mg/dL, these issues become very relevant. Standardization to ensure the validity and comparability of future data remains important.

Nutritional Support in the Era of Tight Glucose Control: What Do We Do with all of This?

Understanding the limitations of the data that are available, the argument is still compelling that moderate glucose control may be beneficial in the ICU, and both hypoglycemia and extreme hyperglycemia may be harmful. As increasing caloric deficits are commonly associated with poor outcomes, nutritional support also remains an area of critical care that can impact glucose levels [34]. Concerns that carbohydrate and nutrient provision in the setting of impaired substrate utilization and metabolic derangement might contribute to poor glycemic control are understandable when providing nutritional support in the ICU. Both nutritional support and glycemic control should be addressed during the initial evaluation of the critically ill patient, and reassessed throughout the patient's hospital stay.

Enteral Nutrition

Caloric provision through the enteral route, either oral or through nasoenteric access, is the appropriate mode of nutritional support in most hemodynamically stable hospitalized patients with a functioning and intact gastrointestinal tract. Unfortunately, many critically ill patients are metabolically abnormal at the time of presentation. To this end, the traditional approach of nothing taken orally the night prior to elective surgery has been challenged in recent years by the concept of carbohydrate loading to ensure the patient is metabolically "primed" prior to operative stress. Oral liquid carbohydrate formulations appear to be safe without substantially increasing the risk of perioperative aspiration [35]. Among the reported benefits, RCTs have demonstrated decreased length of stay, trends toward earlier return of bowel function, improved preservation of skeletal muscle mass, and improved functional capacity when compared to more traditional approaches, although these trials are small [36 – 40]. This has been incorporated into specific protocols designed for the global care of the postoperative colorectal-surgical patient with some success [37]. In addition, when combined with early postoperative enteral support, reduced insulin resistance, and improved glycemic control have been observed [38]. This implies some advantage to avoiding the accentuation of the hyperglycemic stress response associated with operative intervention by minimizing the prestress fasting state. By extension, avoiding the poststress fasting state may also be beneficial. A small randomized trial demonstrated no change in mean-blood glucose, and little change in insulin resistance through the early initiation of enteral nutrition (EN) in patients undergoing major colorectal surgery [38]. This demonstrated the feasibility of achieving both aggressive nutritional support and glycemic control in postoperative patients. Further trials and continuing educational efforts are warranted to garner the support of all parties involved in perioperative care of the critically ill patient, including anesthesiologists, surgeons, and surgical/medical hospitalists, for these principles to be realistically applied.

Several feeding strategies have been attempted to better avoid hyperglycemia, but have generally been unsuccessful. Increasing the ratio of calories given through fat provision, relative to carbohydrate provision, when providing enteral support is one theoretically intriguing approach. One study demonstrated slightly reduced glucose levels when using a 40% carbohydrate, 40% fat, 20% protein formula when compared to standard 50% carbohydrate, 30% fat, 20% protein formula. However, although tight glycemic control was not a specific target of the study, mortality, length of stay, and infectious complications were not statistically different between the groups [41]. Specifically designed formulas for both diabetic patients, and patients requiring prolonged ventilatory support have been designed

applying similar principles, with higher concentrations of calories derived from fats. These formulas are not routinely recommended, even for their intended patient populations, by the American Society of Parenteral and Enteral Nutrition (ASPEN) due to the paucity of data demonstrating their effectiveness, and probably have no role in treating the critically ill patient [42••].

A prudent approach, utilizing the available data, to treat the critically ill patient who is unable to be fed orally involves the administration of standard enteral formulas, except in those patients who are appropriate candidates for immune-enhancing formulas. Some data support the use of immune-enhancing formulas in trauma, severe burns, and major gastrointestinal surgery in an attempt to reduce infectious complications and shorten length of stay [42••]. It should be noted that the majority of immune-enhancing formulas are composed of slightly higher protein content (25%), and lower carbohydrate content (45%). Clearly, the provision of enteral support should not be avoided or reduced in an attempt to regulate glucose levels. An appropriate target for caloric provision (20 – 25 kcal/kg/day) should be the goal, regardless of the formula that is used. Furthermore, the inappropriate cessation of nutritional support during IIT dramatically increases the risk of hypoglycemia with resultant consequences.

Parenteral Nutrition

PN is an important tool in the nutritionist's armamentarium and is life-preserving in those patients who have a true contraindication to EN support. PN has been the focus of much negative commentary of late, due in large part to its widespread inappropriate use. Current Society of Critical Care Medicine (SCCM) and ASPEN recommendations, applicable primarily to patients in the U S, limit the use of PN to patients who have a clear contraindication to EN and are unlikely to tolerate EN during a period of 7 days [42••].

Multiple studies have demonstrated increased nosocomial-infectious complications in patients receiving PN. It has been suggested that many of these studies predated the era of tight glucose control, and that hyperglycemia, rather than PN itself, was responsible for much of the observed increased morbidity. One recent study refuted this hypothesis and concluded that despite adequate glucose control, patients receiving PN were still at increased risk for infectious complications. Matsushima et al. [43•] conducted a prospective cohort study involving 150 surgical intensive care patients in which glucose levels were targeted at 80 – 110 mg/dL. Despite maintaining lower mean glucose values in the PN group (118 mg/dL) when compared to the EN group (125.6 mg/dL), PN patients were 4 times more likely to develop blood-stream infections (BSI) and catheter-related bloodstream infections (CRBSI) [43•]. Obviously, CRBSI may be explained by the obligate requirement for central access in patients receiving PN relative to their EN counterparts, but their conclusions are interesting nonetheless.

The assumption that patients receiving PN experience more hyperglycemic episodes also may not always be true. A recent study by Dan et al. [44] published in 2010 retrospectively compared mean-blood glucose values and daily insulin-dose requirements in 96 mixed medical and surgical ICU patients receiving EN and PN. The PN population had a longer length of ICU stay and received more daily calories than the EN group, but did not require more insulin or have higher mean-blood glucose values. An interesting side note to this study was that the PN patient population was divided into a dextrose-based PN group and a "balanced" glucose plus lipid solution group.. Interestingly, when these groups were compared, they found no difference in these particular parenteral formulations with regard to the above variables, suggesting that adjusting the components of the PN may not improve glycemic control [44]. Hyperglycemia during the use of PN may be a marker for disease

severity. A retrospective study involving 450 patients by Lin et al. [45] observed increased mean-blood glucose values as little as 10 mg/dL in patients receiving PN correlated with statistically significant increases in cardiac risk, acute renal failure, and respiratory failure.

When a patient requires parenteral support, increased attention clearly must be given to glycemic variability as well as hypoglycemic and hyperglycemic episodes. When using PN, a rapid “step-up” approach has been advocated by one study comprised of an initial rate of 10 mL/h (100 kcal) with advancement of 10 mL/h every 4 hours to the target 1 kcal/kg/h used in conjunction with a nurse-driven glucose regulation program [46]. The required insulin dose rose from 1.1 to 2.9 units/h, but less than 5% of measured glucose values were greater than 180 mg/dL.

The sum of these studies suggests that the use of PN and adequate glucose control are not mutually exclusive. In fact, these patients may be more similar to the Leuven patients, and may benefit from a stricter adherence to glycemic control protocols. Patients in whom PN is appropriate have already been self-selected as at high risk for infectious complications and increased morbidity. Care must be taken not to contribute further risk by withholding appropriate caloric provision, or failing to administer adequate glycemic control.

Conclusions

The care of the critically ill patient has become increasingly more complex and the data governing decisions regarding care continue to evolve. The call to arms initiated by the Leuven study has appropriately raised concern over unchecked and poorly controlled hyperglycemia in the ICU. The controversy surrounding the exact values of glucose that should be targeted and the way in which we monitor and treat these values at the bedside remains ongoing. Nutritional support can be initiated early in many cases, and improved glucose control compared to historical levels should be the goal in all critically ill patients. Tight glycemic control cannot routinely be advocated for most groups of surgical patients and more work needs to be performed to identify patient populations that may benefit. Standard or immune-enhancing formulas may be appropriate in certain patient populations, and diabetic or high fat-to-carbohydrate ratios in enteral form are of little benefit. Finally, should PN be required, moderate glucose control is achievable and balanced carbohydrate-fat solutions have not been demonstrated to be more effective.

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