Published in final edited form as:

Curr Opin Gastroenterol. 2010 March ; 26(2): 152–155. doi:10.1097/MOG.0b013e32833663af.

Near-normal glycemia for critically ill patients receiving nutrition support: Fact or folly

Dominic Reeds, M.D.

Center for Human Nutrition, Washington University School of Medicine, St. Louis, MO

Abstract

Purpose of review—In critically ill patients, nutrition support may be a life-saving intervention, but is not without risk. Adverse metabolic changes including hypertriglyceridemia and hyperglycemia are common. Hyperglycemia is associated with adverse outcomes, in particular infection. Four major studies have addressed whether near normal-glycemia (80–110 mg/dl) in this clinical setting improves outcomes compared to blood sugars of ~150mg/dl. The purpose of this review is to determine if tight glycemic control is superior to moderate glycemic control (150mg/dl) in critically ill patients receiving nutrition support.

Findings—Initial data conducted in post-surgical patients suggested that near-normal glycemia dramatically improved outcomes compared to moderate glycemic control. However, three recent studies were unable to duplicate these results and suggest that the benefits of tight-glycemic control may be limited to post-surgical patients and that the controlling hyperlipidemia and overfeeding may improve outcomes more than tight control of blood sugars. Furthermore, near-normal glycemic control caused frequent hypoglycemia and in some cases worsened outcomes.

Summary—Glycemic control to ~150mg/dl is not inferior to near-normal glycemia in critically ill patients requiring nutrition support, and is clearly safer. Lipid changes caused by insulin infusion may improve outcomes more than glycemic control itself and prevention of hypertriglyceridemia should be a major focus of clinical care.

Keywords

Glycemic control; nutrition support; diabetes

Introduction

Hyperglycemia, defined arbitrarily as a blood glucose level greater than 99mg/dl, is common in critically ill patients, and particularly in those receiving TPN. As the population ages and the prevalence of overweight/obesity increases, the incidence of hyperglycemia during hospitalization may be expected to rise. Hyperglycemia has been shown to be associated with increased morbidity and mortality in a variety of disease states including critical illness [1], stroke [2], myocardial infarction [3–5] and trauma [4]. It is likely that host risk factors (obesity, age, family history) and neurohormonal changes associated with illness are responsible for hyperglycemia by inducing peripheral insulin resistance and impairing pancreatic beta-cell function. TPN may further worsen hyperglycemia because of the loss of the normal in cretin response to oral feeding.

Relationship between glycemic control and outcomes

Because of the association between hyperglycemia and adverse outcomes, four large, prospective studies have been performed to determine whether lowering the average blood sugar with intensive insulin therapy (IIT) is associated with improved morbidity and mortality in critically ill patients (Table).

The first of these studies conducted by Van den Berghe et al (Leuven1) compared outcomes in a cohort of predominantly cardiothoracic ICU patients [6]. The goal in the intensive insulin treatment (IIT) group was to achieve blood sugars of 80–110mg/dl compared to standard of care (BG 180–200 mg/dl). The IIT group had lower average blood sugars (103 ± 19 vs 153 ± 33 mg/dl) and a higher rate of hypoglycemia (7 vs 1%). The IIT group had a ~45% relative risk reduction in mortality (8% vs 4.6%) and a 46% lower relative risk of blood stream infection suggesting that treating hyperglycemia improves mortality by reducing infections rate. Subsequently similar mortality benefits were reported by two other groups in both medical ICU and surgical ICU patients [7, 8]. Unfortunately, both these latter studies were observational and used historical control groups for comparison, limiting their validity. A follow-up study by Van den Berghe et al (Leuven 2) evaluated benefits of IIT in **medical** ICU patients [9]. In this study, despite lower average blood sugars with IIT (100 vs 155 mg/dl), no mortality benefit was seen. However benefit was seen for IIT in the surrogate outcomes of ICU length of stay and new onset of renal failure.. Brunkhorst et al. prospectively evaluated the effect of IIT to achieve normoglycemia (BG 80–110 mg/dl) in more than 500 septic patients [10]. Mean blood sugars were again lower in the IIT group than the control group (112mg/dl vs 151mg/dl) however there was no apparent mortality benefit and hypoglycemia was four times more common in the IIT group (17 vs 4%). The recently completed NICE-SUGAR study evaluated the benefits of IIT in achieving near normal glycemia in 6100 patients who were admitted to medical or surgical ICUs[11]. Groups were randomized to either BG<180mg/dl (control group) or 81–108 mg/dl (IIT group). Blood sugar was lower in the IIT than control group (115 ± 18 vs 145 ± 26 mg/dl) and hypoglycemia was more common in IIT than control (6.8 vs 0.5%). Surprisingly, the odds ratio for death in the IIT group was 1.14 (P=0.02), and IIT conferred a 2.5% absolute increase in mortality.

Why the differences in outcomes?

The subject of why these four similar studies produced conflicting results has been perplexing. The initial Leuven study was conducted in surgical ICU patients while the other three studies were performed in medical and surgical ICU settings. This suggests that perhaps post-surgical patients, benefit more from achieving normoglycemia. NICE-SUGAR and Brunkhorst found no differences in outcomes on the basis of recent surgical procedure indicating that recent surgical history is not solely responsible for the differences in outcomes between the studies. Studies conducted almost 20 years ago showed that routine use of TPN in malnourished post-surgical patients increased infection rates, possibly related to TPN-induced hyperglycemia [12]. It should be noted however that the standards of care for catheter site hygiene have dramatically improved since the publication of this early study, so that the overall impact of hyperglycemia on catheter-associated sepsis may have been overestimated. Therefore studies in which most patients are post-surgical AND receive at least some parenteral nutrition (Leuven 1) are more likely to show benefit from tighter glycemic control than studies conducted in a mixed MICU/SICU setting in which 50% of patients were receiving enteral nutrition (NICE-SUGAR, Brunkhorst, Leuven 2).

A key difference between these four studies is the implementation and method of providing nutrition support. Analyzing the studies with respect to caloric delivery requires some assumptions given missing data in all studies. In studies in which protein intake is not

clearly stated, I have assumed 1g/kg/day. As body weight is not given in either of the Leuven studies, assuming an average height of 1.75 meters for men and 1.62 meters for women in each study, average body weight is approximately 72kg. Overfeeding with nutrition support clearly increases morbidity and mortality [12, 13], possibly due in part to hyperglycemia. As most patients in these studies were overweight or obese, their resting energy expenditure was likely lower per kg body weight than that of a patient of normal body weight due to a greater proportion of body weight being composed of relatively metabolically inactive adipose tissue. Accumulating data also suggest that critical illness and recent surgery do not markedly increase energy expenditure above that predicted by the Harris-Benedict equation [14, 15]. Based on the BMI of the patients in each study, it is likely that the patients in both Leuven studies were actually overfed, increasing the likelihood of developing not only hyperglycemia but also metabolic acidosis, hypertriglyceridemia and fatty liver. As noted, overfeeding in post-operative patients is particularly problematic, increasing the rates of infection [12]. It is therefore, not surprising that a predominantly post-surgical group benefited from limitation of hyperglycemia when being overfed, as suggested by Leuven 1. Indeed, it is possible that the benefits of hypocaloric feeding [16] masked any benefit of glycemic control in NICE-sugar and Brunkhorst. It is likely that the benefit of IIT may have disappeared had the patients in Leuven 1 not been overfed.

A final point to consider is that of the metabolic effects of insulin beyond glycemic control. Early studies dating to the 1960s [17], and more recent meta-analyses [18], indicate that an infusion of glucose, insulin and potassium improves outcomes in patients with acute coronary syndromes, suggesting that it is not hyperglycemia *per se* that worsens outcomes but possibly that hyperinsulinemia confers metabolic and clinical benefit. Insulin has a number of potentially helpful actions in critical illness; it suppresses lipolytic rate, sequesters fatty acids into intracellular lipid stores, lowers plasma and possibly intracellular free fatty acid concentration which may reduce tissue 'lipotoxicity', and by limiting fatty acid availability, increases myocardial glucose utilization. These changes may improve left ventricular function and cardiac efficiency. Insulin may also attenuate the increase in whole-body proteolytic rate that occurs in critical illness, ameliorating loss of lean body mass which is tightly related to outcome. Insulin also rapidly reduces plasma triglyceride concentration. Post-hoc analysis of data from >350 patients who had ICU stays over 7 days in Leuven 1 showed that plasma TG rose ~80% from baseline in the control group compared to no change with IIT [19]. There was 'an almost linear relationship between TG concentration and mortality. Indeed patients with TG <100 had a mortality rate of only 5% compared to a 40% mortality rate in patients with TG >300 mg/dl. While hyperglycemia increases plasma TG, overfeeding and TPN are both well known to increase the risk of hypertriglyceridemia. Taken together, these results suggest that overfeeding in Leuven I contributed to metabolic disturbances that could be attenuated by insulin infusion. Therefore while benefit was seen, this was due to metabolic actions of insulin other than glycemic control.

Is near-normal glycemia dangerous?

While focus has been placed on hyperglycemia, the relationship between mean blood glucose level and outcomes is a J-shaped curve in which both hyperglycemia and hypoglycemia are associated with poorer outcomes [20]. Bagshaw evaluated the relationship between average blood sugar and outcomes in a cohort of 66,000 patients admitted to the ICU and found that blood sugars in the highest (adjusted odds ratio 1.10) and lowest (adjusted odds ratio 1.29) were both associated with worse outcomes. These findings have been validated by both NICE-SUGAR and Brunkhorst's studies, indicating that the risk of

hypoglycemia is dramatically greater with IIT and suggesting that this could contribute to the poorer outcomes with IIT seen in NICE-SUGAR.

Conclusions

From these studies, some conclusions can be drawn. Overfeeding, and probably hyperglycemia, increase risk of infection in surgical patients. Near-normal glycemia improves outcomes in this setting however, limiting nutrition support to appropriate patients, and prevention of overfeeding are likely to be equally effective and safer. If patients are not overfed, then it is likely that there is no dramatic benefit from achieving normoglycemia with IIT in critical illness compared to BG<150–180mg/dl. There is clear evidence of risk with IIT and in the absence of clear data showing benefit, particularly in medical ICU patients, maintaining BG <180mg/dl but not less than ~100mg/dl is likely to result in better outcomes. Insulin action on lipid and protein metabolism could explain the beneficial effects of early IIT and should be evaluated with larger prospective studies.

Acknowledgments

Grant Support: American Society for Nutrition, DK56431 (Clinical Nutrition Research Unit)

References

1. Krinsley JS. Association between hyperglycemia and increased hospital mortality in a heterogeneous population of critically ill patients. *Mayo Clin Proc.* 2003; 78(12):1471–8. [PubMed: 14661676]
2. Bruno A, et al. Admission glucose level and clinical outcomes in the NINDS rt-PA Stroke Trial. *Neurology.* 2002; 59(5):669–74. [PubMed: 12221155]
3. van der Horst IC, et al. Persistent hyperglycemia is an independent predictor of outcome in acute myocardial infarction. *Cardiovasc Diabetol.* 2007; 6:2. [PubMed: 17284309]
4. Vogelzang M, et al. Hyperglycemia has a stronger relation with outcome in trauma patients than in other critically ill patients. *J Trauma.* 2006; 60(4):873–7. discussion 878–9. [PubMed: 16612311]
5. Goyal A, et al. Prognostic significance of the change in glucose level in the first 24 h after acute myocardial infarction: results from the CARDINAL study. *Eur Heart J.* 2006; 27(11):1289–97. [PubMed: 16611669]
- *6. van den Berghe G, et al. Intensive insulin therapy in the critically ill patients. *N Engl J Med.* 2001; 345(19):1359–67. The initial study that supported tight glycemic control. [PubMed: 11794168]
7. Krinsley JS. Effect of an intensive glucose management protocol on the mortality of critically ill adult patients. *Mayo Clin Proc.* 2004; 79(8):992–1000. [PubMed: 15301325]
8. Furnary AP, et al. Continuous insulin infusion reduces mortality in patients with diabetes undergoing coronary artery bypass grafting. *J Thorac Cardiovasc Surg.* 2003; 125(5):1007–21. [PubMed: 12771873]
- *9. Van den Berghe G, et al. Intensive insulin therapy in the medical ICU. *N Engl J Med.* 2006; 354(5):449–61. Initial study focused on glycemic management in medical ICU patients. [PubMed: 16452557]
- **10. Brunkhorst FM, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med.* 2008; 358(2):125–39. Article demonstrating evidence of risk with tight glycemic control. [PubMed: 18184958]
- **11. Finfer S, et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med.* 2009; 360(13):1283–97. Most recent study evaluating the efficacy of tight glycemic control in critical illness. [PubMed: 19318384]
- *12. The Veterans Affairs Total Parenteral Nutrition Cooperative Study Group. . Perioperative total parenteral nutrition in surgical patients. *Engl J Med.* 1991; 325(8):525–32. Seminal paper that reported the subsets of patients who may benefit from perioperative nutrition.

13. Klein CJ, Stanek GS, Wiles CE. 3rd, Overfeeding macronutrients to critically ill adults: metabolic complications. *J Am Diet Assoc.* 1998; 98(7):795–806. [PubMed: 9664922]
14. Miles JM. Energy expenditure in hospitalized patients: implications for nutritional support. *Mayo Clin Proc.* 2006; 81(6):809–16. [PubMed: 16770981]
15. Sandstrom R, et al. The effect of postoperative intravenous feeding (TPN) on outcome following major surgery evaluated in a randomized study. *Ann Surg.* 1993; 217(2):185–95. [PubMed: 8439216]
16. Casadei E, et al. Effects of hypocaloric feeding on clinical outcome in ICU patients. 2006:217.
17. Mittra B. Potassium, glucose, and insulin in treatment of myocardial infarction. *Lancet.* 1965; 2(7413):607–9. [PubMed: 4157501]
18. Fath-Ordoubadi F, Beatt KJ. Glucose-insulin-potassium therapy for treatment of acute myocardial infarction: an overview of randomized placebo-controlled trials. *Circulation.* 1997; 96(4):1152–6. [PubMed: 9286943]
- **19. Mesotten D, et al. Contribution of circulating lipids to the improved outcome of critical illness by glycemic control with intensive insulin therapy. *J Clin Endocrinol Metab.* 2004; 89(1):219–26. Interesting post-hoc analysis of data from Leuven I suggesting that glycemic control may not be responsible for the benefit of insulin infusion in critical illness. [PubMed: 14715853]
20. Bagshaw SM, et al. Early blood glucose control and mortality in critically ill patients in Australia. *Crit Care Med.* 2009; 37(2):463–70. [PubMed: 19114915]

Table 1

	Leuven 1	Leuven 2	Brunkhorst	NICE-SUGAR
Population	SICU	MICU	Mix	Mix
% of patients receiving TPN	Not shown	~30%	50%	30%
Kcal/kg/day	29	30	20	15
Benefit?	Y	Y	N	N