Advances in Surgery 47 (2013) 287–297
ADVANCES IN SURGERY

Stress-induced Hyperglycemia
Is It Harmful Following Trauma?

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Keywords

• Trauma • Hyperglycemia • Critical care • Glycemic control

Key points

- Stress-induced hyperglycemia (SIH) is common after severe trauma and results from an imbalance of glucose production and glucose clearance induced by increased circulating levels of stress hormones and cytokines.
- SIH is associated with increased morbidity and mortality in certain medical conditions and trauma patients, although no direct causative effect has been proved.
- Prospective clinical trials have provided conflicting evidence regarding the use of tight glycemic control regimens. No prospective, randomized controlled clinical trials have been performed specifically evaluating the trauma population.
- The cause of hyperglycemia may be critically important in establishing those that may benefit from tight glycemic control regimens.
- Most institutions currently use moderate glucose control protocols. Properly designed prospective clinical trials and future technology limiting glucose variability will further clarify the appropriate levels of glucose control that result in improved outcomes.

INTRODUCTION

Hyperglycemia is well recognized as a normal metabolic stress response [1]. In settings of acute illness or injury, it has been termed stress-induced hyperglycemia (SIH) and has been defined as a transient plasma glucose level higher than 200 mg/dL in patients who are normally euglycemic. Ultimately, SIH results from an overabundance of glucose production relative to glucose clearance. More specifically, the cause of SIH is secondary to a state of enhanced glucose

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0065-3411/13/$ – see front matter
http://dx.doi.org/10.1016/j.yasu.2013.03.002 Published by Elsevier Inc.

production, diminished insulin production, and insulin resistance in peripheral tissues as a result of increases in stress hormones and cytokines (Table 1) [1,2]. Therefore, the more ill or seriously injured the patient, the higher the glucose levels secondary to the increased presence of stress hormones. This state typically persists until inflammatory mediators have decreased and the catabolic state subsides. Typical risk factors for SIH in acute trauma patients include large injury burden indicated by higher injury severity score (ISS), higher base deficit, and higher lactic acidosis [3,4]. Historically, these responses were believed to be protective to patients in acute phases of inflammation. However, in the last decade, much attention has been focused on the impact of hyperglycemia and whether aggressive treatment aimed at controlling serum glucose levels improves outcomes. SIH has been associated with several conditions including myocardial infarction [5–7], stroke [8,9], and trauma [10–12]. Published studies that evaluated the association between SIH and outcomes in these patients have consistently shown higher morbidity and higher mortality rates. However, it is still unclear whether SIH has a direct causative effect leading to worse outcomes, or is merely a marker of more severe disease. Existing studies do provide some mechanistic evidence for acute glucose toxicity, particularly in the setting of ischemia-reperfusion, which may be induced by damage to mitochondria that take up glucose in direct proportion to circulating blood glucose levels [13–15]. In the search for treatment regimens to lower morbidity and mortality in patients requiring intensive care, conflicting evidence in the treatment of hyperglycemia has emerged. This article focuses on hyperglycemia in the severely

Table 1
Mechanisms of hormones and cytokines in mediating stress-induced hyperglycemia

Hormone	Mechanism
Glucagon	Increased gluconeogenesis
	Increased hepatic glycogenolysis
Epinephrine	Skeletal muscle insulin resistance by altering postreceptor signaling
	Increased gluconeogenesis
	Increased skeletal muscle and hepatic glycogenolysis
	Increased lipolysis, increased free fatty acids
	Direct suppression of insulin secretion
Norepinephrine	Increased lipolysis
	Increased gluconeogenesis but hyperglycemia not marked except at high concentrations
Growth hormone	Skeletal muscle insulin resistance
	Increased lipolysis
	Increased gluconeogenesis
Tumor necrosis factor	Skeletal muscle insulin resistance, altered postreceptor signaling
	Hepatic insulin resistance

Data from McCowen KC, Malhotra A, Bistrian BR. Stress-induced hyperglycemia. Crit Care Clin 2001;17(1):107–24.

injured trauma patient, and whether available evidence currently supports the use of protocols aimed at aggressive glucose control.

HYPERGLYCEMIA: IMPACT AND APPROACH TO TREATMENT

Morbidity and mortality associated with hyperglycemia

Initial interest in hyperglycemia in the trauma patient began after the realization of worse outcomes in medical patients who had developed SIH. SIH has been associated with increased mortality and a higher incidence of congestive heart failure and cardiogenic shock in patients after myocardial infarction [5–7]. Stroke victims likewise have demonstrated higher mortality associated with SIH, and having worse odds of desirable neurologic outcomes as glucose levels increased with SIH [8,9]. As one of the more common metabolic derangements in severely injured patients, multiple efforts to examine the potential harm of hyperglycemia associated with the severely injured trauma patient have been undertaken. In 2003, Yendamuri and colleagues [10] first published a retrospective study that evaluated the association of admission hyperglycemia in trauma patients with outcome. They demonstrated that an admission glucose level greater than 200 mg/dL was independently associated with an increase in mortality in trauma patients. This finding was likewise true for a mild level of hyperglycemia (glucose >135 mg/dL). Additionally, the study found that hyperglycemia was a predictor of infectious complications in the form of pneumonia, urinary tract infections, wound infections, and bacteremia. Similarly, Sung and colleagues [11] prospectively evaluated 1003 trauma patients over a 2-year period who were admitted to the intensive care unit (ICU) or intermediate care unit of their level I trauma center. Patients were stratified into two groups based on admission glucose levels greater than or less than 200 mg/dL. To eliminate confusion between diabetic hyperglycemia (DH) and SIH, patients with history of diabetes were excluded from the study. They determined that a glucose level greater than or equal to 200 mg/dL was an independent predictor of increased mortality and infection. Laird and colleagues [12] evaluated the relationship of trauma outcomes in the ICU population differentiated by increasing levels of hyperglycemia on presentation. This retrospective study excluded patients with a known history of diabetes. For the 516 patients in the study group, hyperglycemia was evaluated at three levels of admission glucose (>110, >150, and >200). They found that only glucose levels greater than 200 mg/dL were associated with higher mortality and infection rates, leading to the conclusion that glucose levels should be maintained below 200 mg/dL but potentially not to the level of less than 110 mg/dL. Vogelzang and colleagues [16,17] defined the hyperglycemic index and applied it in a retrospective evaluation of 6099 surgical patients. Hyperglycemic index was developed by these investigators as a way of reflecting the magnitude of hyperglycemia in critically ill patients over time. Various surgical patients were evaluated in the study to include vascular, gastrointestinal, liver transplant, trauma, and other miscellaneous surgical patients. Their results demonstrated the relationship between hyperglycemia and mortality depended on the reason for admission. Trauma patients with hyperglycemia had a more pronounced

mortality than for any other type of critically ill surgical patients. When comparing the trauma subgroup, trauma nonsurvivors had a statistically higher glucose level that was persistently elevated throughout the ICU stay compared with trauma survivors.

Bochicchio and colleagues [18] examined the effect of persistent hyperglycemia on critically ill trauma patients over the first week of admission. Patients were stratified based on glucose levels from Days 1 to 7 into low (0–139 mg/dL), medium (140–219 mg/dL), and high (≥220 mg/dL) groups. Patients were further stratified by glucose control pattern (all low, all moderate, all high, improving, worsening, and highly variable). There was no standardized protocol for glucose management with management being left at the discretion of the treating physicians. All patients that had patterns of glucose control versus the low group demonstrated a statistically significant higher odds ratio for mortality when adjusted for age and ISS. The worsening and highly variable glucose control groups were the most predictive for increased mortality and infectious morbidity suggesting persistently elevated or increasing stress hormone activity in these patients.

Treatment of hyperglycemia in critically ill patients

Defining appropriate treatment of SIH remains an area of ongoing investigation. Van den Berghe and colleagues [19] prospective randomized controlled study examining intensive insulin therapy in surgical ICU patients was provocative and has led to additional studies designed to duplicate and validate their findings. The original study enrolled 1548 patients consisting of primarily surgical patients, most of whom had undergone some form of cardiac surgery. Those patients were randomized to either an intensive insulin therapy regimen (maintenance of glucose levels between 80 and 110 mg/dL) or a conventional regimen (infusion of insulin only if the blood glucose exceeded 215 mg/dL with maintenance of glucose levels between 180 and 200 mg/dL). Intensive therapy resulted in a reduction of mortality from 8.6% to 4% (reduction of 34%) and a reduction in overall morbidity. A subsequent study by Van den Berghe and colleagues [20] in medical ICU patients showed no improvement in overall mortality using the same protocol for glucose control as the original study. However, issues with the safety of tight glycemic control have been generated because profound hypoglycemia, defined as blood glucose less than 40 mg/dL, was identified as an independent risk factor for death in the latter study. Following this, several studies and meta-analyses were performed that had mixed results. However, although not widely adopted, several professional organizations supported and recommended tight glucose control (TGC) regimens to treat hyperglycemia [21].

The prospective, randomized controlled NICE-SUGAR study was subsequently performed to further delineate the optimal target range for blood glucose level in critically ill patients [22]. This study evaluated a mix of surgical and medical ICU patients and had death from any cause up to 90 days after randomization as its primary outcome. Patients were randomized to receive either intensive glucose control (target blood glucose range, 81–108 mg/dL) or conventional control (blood glucose ≤180 mg/dL). The results from this

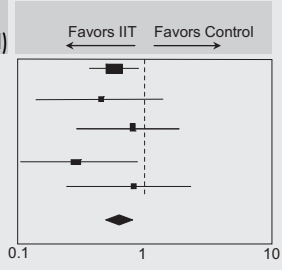
trial showed mortality was higher in the intensive arm than in the conventional glucose control arm. Based on their results, the authors suggested abandoning the lower target of glycemic control. However, the NICE-SUGAR study contained a mix of medical and surgical patients. Subsequent studies have suggested that certain subgroups of patients may have benefitted from tighter glucose control. Griesdale and colleagues [23] conducted a meta-analysis of randomized published studies (NICE-SUGAR included) examining the affect of tight glycemic control versus more conventional glucose management in ICU patients. To be included, the trials had to contain mortality data. The results demonstrated that patients in medical ICUs or mixed ICUs received no benefit in mortality in the tight glycemic control arm compared with a conventional control arm, whereas the surgical ICU subgroup, which included trauma patients, seemed to benefit from TGC (Table 2).

Treatment of hyperglycemia in trauma patients

Studies focusing strictly on trauma patients have been performed. However, to date no prospective randomized studies have been completed solely evaluating this patient population. Most of the current data evaluating the effects of treatment of hyperglycemia on outcomes in trauma use historical controls to compare eras before and after implementation of a protocol aimed at hyperglycemic control. For example, Scalea and colleagues [24] evaluated outcomes before and after the implementation of a TGC regimen and showed improved outcomes. They studied patients during the first week of ICU admission and compared the preintervention 24-month period (no TGC) with the 24-month period after institution of the TGC protocol. The protocol goal was to maintain blood glucose between 100 and 150 mg/dL, as opposed to the 80 to 110 mg/dL originally suggested by Van den Berghe [19]. When controlling for ISS, age,

Table 2
Risk ratios of mortality in clinical trials comparing IIT with conventional glycemic control in surgical patients

Study	Number of Deaths/Total Number of Patients IIT	Control	Risk Ratio (95% CI)
Van den Berghe et al [19]	55/765	85/783	0.66 (0.48–0.92)
Grey et al [35]	4/34	6/27	0.53 (0.17–1.69)
Bilotta et al [36]	6/40	7/38	0.81 (0.30–2.20)
He et al [37]	7/150	6/38	0.30 (0.11–0.83)
Bilotta et al [38]	5/48	6/49	0.85 (0.28–2.60)
All surgical ICU patients	77/1037	110/935	0.63 (0.44–0.91)



Abbreviations: CI, confidence interval; ICU, intensive care unit; IIT, intensive insulin therapy.

Adapted from Griesdale DE, de Souza RJ, van Dam RM, et al. Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data. CMAJ 2009;180(8): 821–7.

and gender, patients with TGC experienced better outcomes in terms of morbidity, length of stay, and mortality.

These results, however, have not been duplicated in other trauma studies. Wahl and colleagues [25] evaluated results in their population of critically ill trauma patients before and after implementation of a stricter glucose control regimen. In their study, the targeted glucose level was less than 140 mg/dL. Although they showed that mean glucose levels were lower and the percentage of patients with all daily values less than the target was higher, mortality, hospital, and ICU length of stay and ventilator days did not differ between the eras compared. The incidence of severe hypoglycemia (glucose <40 mg/dL) was low and not statistically different between the two treatment approaches. Toschlog and colleagues [26] retrospectively looked at a 6-month period before and after implementation of a computerized hospital insulin protocol (CHIP) to maintain euglycemia. They evaluated glycemic control and outcome on trauma patients admitted to their ICU during this period. They demonstrated that the pre-CHIP group had a mean glucose of 130 ± 45 versus 116 ± 39 mg/dL after institution of the protocol. This modest lowering of mean glucose level was statistically significant. However, although infectious morbidity and length of stay improved in the post-CHIP group, mortality actually worsened. More recently, Kutcher and colleagues [27] reported on outcomes associated with three nonoverlapping approaches to glucose control over a 9-year period. During this time, their approach to glucose control evolved from "relaxed" (targeted blood glucose <180 mg/dL), to "aggressive" (targeted blood glucose range between 80 and 120 mg/dL), and finally to "moderate" (targeted blood glucose range of 80–140 mg/dL with institution at blood glucose ≥160 mg/dL). The results of their analysis revealed no difference in the incidence of multiorgan failure or mortality among the three groups.

DOES THE CAUSE OF HYPERGLYCEMIA MATTER?

The physiologic state associated with SIH is much different than that of DH, a chronic process associated with elevated glucose levels over time. This prolonged hyperglycemia subsequently leads to microvascular changes that result in diabetic disease manifestations (eg, coronary artery disease, nephropathy, and peripheral vascular disease) leading to morbidity and mortality. Because DH is the stimulus that causes the disease manifestations, effective treatment over the long term improves outcomes in these patients. In patients with DH, chronic exposure to elevated glucose levels may have led to adaptive changes at the cellular level aimed at abrogating the toxic effects of elevated glucose over time. Therefore, therapies aimed at lowering blood glucose levels in these patients may not be as beneficial. In contrast, SIH is an acute process initiated by stress hormone and cytokine release secondary to tissue damage. In this situation, because identification and initiation of treatment of hyperglycemia happen relatively soon after the initial insult, the time window for benefit of glycemic control to avoid acute glucose toxicity may not have passed. This potential differential effect may explain the disparity in results when examining

tight glycemic control regimens in the surgical versus the medical ICUs [19,20]. In summary, the mechanism for potential negative impact in these two hyperglycemia states differs and their impact on outcomes after trauma likewise may not be the same.

Whether the underlying physiologic cause of the hyperglycemia, or simply the glucose level itself regardless of mechanism, has more of an impact on outcomes has not been extensively studied. Delineating whether the glucose elevation is a response to stress, secondary to poorly controlled or occult diabetes, or a mixture of both is difficult to ascertain. Most trauma studies evaluating glucose control exclude diabetic patients or make no attempt to identify patients with occult diabetes. This makes interpretation of the results of these studies difficult because the source of the hyperglycemia may determine whether a treatment regimen aimed at controlling glucose levels has an effect on outcome. This is significant given the large number of patients who present with occult diabetes. Approximately 8.3% of the United States population (25.8 million people) has diabetes, whether previously diagnosed or undiagnosed based on data from the National Center for Chronic Disease Prevention and Health Promotion of the Centers for Disease Control and Prevention [28]. It has been estimated that upward of 25% of all patients suffering from diabetes have no knowledge of their disease and thus have occult diabetes mellitus (ODM). Fortunately, new standards for the diagnosis of diabetes make it relatively easy to identify trauma patients who present with ODM. Diabetes can be diagnosed by several laboratory studies (Box 1). However, the American

Box 1: Criteria for diagnosis of diabetes

HbA_{1c} $\geq$6.5%: The test should be performed in a laboratory using a method that is certified by the National Glycohemoglobin Standardization Program and standardized to the Diabetes Control and Complications Trial assay[a]

or

Fasting plasma glucose $\geq$126 mg/dL (7 mmol/L): Fasting is defined as no caloric intake for at least 8 h[a]

or

2-h plasma glucose $\geq$200 mg/dL (11.1) mmol/L during an oral glucose tolerance test: The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water[a]

or

In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose $\geq$200 mg/dL (11.1 mmol/L)

[a] In the absence of unequivocal hyperglycemia, criteria 1 to 3 should be confirmed by repeat testing.

Data from American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2012;35(S1):8.

Diabetes Association has recently stated in its 2012 position paper that a glycosylated hemoglobin A_{1C} (HbA_{1c}) level greater than or equal to 6.5% is diagnostic for DM regardless of whether or not a history of hyperglycemia is present [29]. HbA_{1c} reflects average blood glucose levels over a 2- to 3-month period of time and is a widely used marker of chronic glycemic states.

In the trauma literature, only two studies have evaluated the true incidence of pre-existing diabetes in acutely injured patients. Kopelman and colleagues [4] prospectively evaluated trauma patients with no history of DM that presented with elevated glucose levels ($\geq$110 mg/dL) to find that nearly one-quarter of these patients had ODM. These studies are consistent with Centers for Disease Control and Prevention estimates of overall incidence of diabetes in the US population and rate of ODM in the diabetic population. Kerby and colleagues [3] retrospectively evaluated 5117 trauma patients admitted to a level 1 trauma center over a 2-year period to further define hyperglycemic populations and compare the impact of SIH versus DH on outcomes in trauma patients. HbA_{1c} levels were ascertained in addition to admission glucose and comorbidity data. In this study, approximately 8.7% of the study population (446 patients) was diagnosed with DM, of which nearly 25% (137 patients) had no prior history of DM and were newly diagnosed using HbA_{1c} values. When comparing patients with isolated SIH with those with DH (patients with hyperglycemia with known diabetes or ODM), the results showed that patients with SIH, and not those with DH, had higher mortality after trauma. This study suggests that hyperglycemia has a separate and more severe effect on mortality outcome in nondiabetic, stressed patients compared with those with hyperglycemia of diabetes. This is true even for patients who present in severe shock (defined as presenting base deficit $\geq$6). Given these results along with the underlying differences in these patient populations as outlined previously, the authors theorized that more strict glucose control protocols would most likely benefit patients with SIH as opposed to those with DH.

FUTURE DIRECTIONS

There have been no definitive prospective, randomized controlled trials evaluating glucose control regimens focused entirely on the trauma population. A properly designed, multi-institutional study of this nature will greatly add to the existing literature and clarify whether more stringent glucose control regimens lead to improved outcomes in trauma patients. Given the high prevalence of ODM in the population, these studies will preferably include prospective evaluations of stress hormones, cytokine levels, and HbA_{1c} levels to aid in determining those presenting with true SIH versus DH. The study should also be designed to either exclude patients with DH from randomization or perform an a priori subgroup analysis on patients only with true SIH. Uniform protocols for glucose monitoring that provide reasonably efficient time to glycemic control while minimizing severe hypoglycemic episodes will also be vital to any prospective evaluation. Several papers outlining various forms of CHIPs have shown them to shorten the time interval to glycemic control while

reducing the frequency of hypoglycemic episodes [26,30–32]. A commercially available product is also available with proved efficacy in surgical ICUs [33,34].

SUMMARY

There is an established association between the presence of SIH and worse morbidity and mortality after trauma. However, given the limitations of existing data, no definitive statements can be made as to whether aggressive treatment of hyperglycemia actually benefits outcome. Although early studies seemed to show a clear benefit in surgical ICU patients, subsequent studies have not duplicated these results. In addition, severe hypoglycemic episodes associated with glycemic control protocols have provided further concern, because they have been associated with higher rates of mortality. These disparate outcomes in prospective, randomized trials have not allowed definitive conclusions to be drawn regarding the exact glucose levels that should be maintained. Regardless, some postinjury control of glucose levels is likely necessary. Without data to support the practice, tight glycemic control keeping glucose levels below 110 mg/dL is likely not necessary and probably detrimental to patient outcome. It seems that a more moderate level of glycemic control, aimed at providing stabilization of glucose levels while reducing hyperglycemic and hypoglycemic events, is being practiced in most institutions. Performance of prospective, randomized trials in the trauma population along with further advancement and refinement of techniques to more precisely reduce glucose variability will further clarify the level of glucose control associated with improved outcomes.

References

[1] McCowen KC, Malhotra A, Bistrian BR. Stress-induced hyperglycemia. Crit Care Clin 2001;17(1):107–24.
[2] Epstein J, Breslow MJ. The stress response of critical illness. Crit Care Clin 1999;15(1):17–33, v.
[3] Kerby JD, Griffin RL, MacLennan P, et al. Stress-induced hyperglycemia, not diabetic hyperglycemia, is associated with higher mortality in trauma. Ann Surg 2012;256(3):446–52.
[4] Kopelman TR, O'Neill PJ, Kanneganti SR, et al. The relationship of plasma glucose and glycosylated hemoglobin A1C levels among nondiabetic trauma patients. J Trauma 2008;64(1):30–3 [discussion: 33–4].
[5] Bellodi G, Manicardi V, Malavasi V, et al. Hyperglycemia and prognosis of acute myocardial infarction in patients without diabetes mellitus. Am J Cardiol 1989;64(14):885–8.
[6] Capes SE, Hunt D, Malmberg K, et al. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. Lancet 2000;355(9206):773–8.
[7] Kosiborod M, Rathore SS, Inzucchi SE, et al. Admission glucose and mortality in elderly patients hospitalized with acute myocardial infarction: implications for patients with and without recognized diabetes. Circulation 2005;111(23):3078–86.
[8] Capes SE, Hunt D, Malmberg K, et al. Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients: a systematic overview. Stroke 2001;32(10):2426–32.
[9] Bruno A, Levine SR, Frankel MR, et al. Admission glucose level and clinical outcomes in the NINDS rt-PA Stroke Trial. Neurology 2002;59(5):669–74.
[10] Yendamuri S, Fulda GJ, Tinkoff GH. Admission hyperglycemia as a prognostic indicator in trauma. J Trauma 2003;55(1):33–8.

[11] Sung J, Bochicchio GV, Joshi M, et al. Admission hyperglycemia is predictive of outcome in critically ill trauma patients. J Trauma 2005;59(1):80–3.
[12] Laird AM, Miller PR, Kilgo PD, et al. Relationship of early hyperglycemia to mortality in trauma patients. J Trauma 2004;56(5):1058–62.
[13] Van den Berghe G. How does blood glucose control with insulin save lives in intensive care? J Clin Invest 2004;114(9):1187–95.
[14] Langouche L, Vanhorebeek I, Vlasselaers D, et al. Intensive insulin therapy protects the endothelium of critically ill patients. J Clin Invest 2005;115(8):2277–86.
[15] Vanhorebeek I, De Vos R, Mesotten D, et al. Protection of hepatocyte mitochondrial ultrastructure and function by strict blood glucose control with insulin in critically ill patients. Lancet 2005;365(9453):53–9.
[16] Vogelzang M, van der Horst IC, Nijsten MW. Hyperglycaemic index as a tool to assess glucose control: a retrospective study. Crit Care 2004;8(3):R122–7.
[17] Vogelzang M, Nijboer JM, van der Horst IC, 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].
[18] Bochicchio GV, Sung J, Joshi M, et al. Persistent hyperglycemia is predictive of outcome in critically ill trauma patients. J Trauma 2005;58(5):921–4.
[19] van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. N Engl J Med 2001;345(19):1359–67.
[20] Van den Berghe G, Wilmer A, Hermans G, et al. Intensive insulin therapy in the medical ICU. N Engl J Med 2006;354(5):449–61.
[21] Garber AJ, Moghissi ES, Bransome ED, et al. American College of Endocrinology position statement on inpatient diabetes and metabolic control. Endocr Pract 2004;10(Suppl 2):4–9.
[22] Finfer S, Chittock DR, Su SY, et al. Intensive versus conventional glucose control in critically ill patients. N Engl J Med 2009;360(13):1283–97.
[23] Griesdale DE, de Souza RJ, van Dam RM, et al. Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data. CMAJ 2009;180(8):821–7.
[24] Scalea TM, Bochicchio GV, Bochicchio KM, et al. Tight glycemic control in critically injured trauma patients. Ann Surg 2007;246(4):605–10 [discussion: 610–2].
[25] Wahl WL, Taddonio M, Maggio PM, et al. Mean glucose values predict trauma patient mortality. J Trauma 2008;65(1):42–7 [discussion: 47–8].
[26] Toschlog EA, Newton C, Allen N, et al. Morbidity reduction in critically ill trauma patients through use of a computerized insulin infusion protocol: a preliminary study. J Trauma 2007;62(6):1370–5 [discussion: 1375–6].
[27] Kutcher ME, Pepper MB, Morabito D, et al. Finding the sweet spot: identification of optimal glucose levels in critically injured patients. J Trauma 2011;71(5):1108–14.
[28] National Diabetes Fact Sheet. Centers for Disease Control and Prevention 2011. Available at: www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf. Accessed January 9, 2013.
[29] American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2012;35(Suppl 1):8.
[30] Vogelzang M, Zijlstra F, Nijsten MW. Design and implementation of GRIP: a computerized glucose control system at a surgical intensive care unit. BMC Med Inform Decis Mak 2005;5:38.
[31] Dortch MJ, Mowery NT, Ozdas A, et al. A computerized insulin infusion titration protocol improves glucose control with less hypoglycemia compared to a manual titration protocol in a trauma intensive care unit. JPEN J Parenter Enteral Nutr 2008;32(1):18–27.
[32] Sood R, Zieger M, Roggy D, et al. The effectiveness of a computerized IV infusion protocol to treat hyperglycemia in burn patients. J Burn Care Res 2012;33(5):638–41.
[33] Saager L, Collins GL, Burnside B, et al. A randomized study in diabetic patients undergoing cardiac surgery comparing computer-guided glucose management with a standard sliding scale protocol. J Cardiothorac Vasc Anesth 2008;22(3):377–82.

[34] Fogel SL, Baker CC. Effects of computerized decision-support systems on blood glucose regulation in critically ill surgical patients. J Am Coll Surg 2013;216(4):828–33.
[35] Grey NJ, Perdrizet GA. Reduction of nosocomial infections in the surgical intensive-care unit by strict glycemic control. Endocr Pract 2004;10(Suppl 2):46–52.
[36] Bilotta F, Spinelli A, Giovannini F, et al. The effect of intensive insulin therapy on infection rate, vasospasm, neurologic outcome, and mortality in neurointensive care unit after intracranial aneurysm clipping in patients with acute subarachnoid hemorrhage: a randomized prospective pilot trial. J Neurosurg Anesthesiol 2007;19(3):156–60.
[37] He W, Zhang TY, Zhou H, et al. Impact of intensive insulin therapy on surgical critically ill patients. Zhonghua Wai Ke Za Zhi 2007;45(15):1052–4.
[38] Bilotta F, Caramia R, Cernak I, et al. Intensive insulin therapy after severe traumatic brain injury: a randomized clinical trial. Neurocrit Care 2008;9(2):159–66.