Glycemic Control in the Intensive Care Unit: Between Safety and Benefit

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Patient safety has become a major global social health problem. Risk/benefit ratios are used widely in all fields of medicine as part of patient safety and quality of care. It is known that patients admitted to the intensive care unit are especially vulnerable to adverse care-related errors as a result of their severe illness and the multiple aggressive interventions in critical care, which also have risk/benefit ratios. For instance, mechanical ventilation can both improve respiratory abnormalities and cause ventilator-related lung injury. Fluid administration can resuscitate a shock state but can cause pulmonary edema. Intensive insulin therapy for tight glucose control may improve outcomes in critically ill patients but may be harmful due to severe hypoglycemia. We focus here on analyses of the literature devoted to some aspects of glycemic regulation among ICU patients.

Very high and very low blood glucose levels are both associated with worse outcomes

GLYCEMIC CONTROL AND IMPACT OF HYPERGLYCEMIA

It is well established that even modest hyperglycemia has a negative impact on a wide range of critically ill patients and is associated with worse outcome [1,2], but whether this association is causal remains unclear. Observational studies have revealed a J-curved relationship between blood glucose and mortality, with a nadir approximately between 5 and 8 mmol/L (90–140 mg/dl). In patients with acute coronary syndrome a similar association has been observed, with lowest risk of mortality at blood glucose levels between 4.4 and 5.5 mmol/L (80–100 mg/dl) [3]. Critically ill medical and surgical patients with admission hyperglycemia and higher mean blood glucose during hospitalization had a higher mortality rate when compared with matched normoglycemic patients [2].

Trauma patients with hyperglycemia on admission or throughout the hospital stay have not only higher mortality but also longer duration of mechanical ventilation and length of ICU stay, and higher rate of infections [4]. The highest blood sugar occurring in the first 24 hours of ICU care among patients with traumatic brain injury is linearly correlated with mortality. It is interesting that such a correlation is closer than the inverse correlation between mean arterial pressure and mortality [5].

The issue of IIT for tight glucose control in the ICU setting has been a matter of debate and controversy over the past decade, especially after the published study of Van den Berghe et al. [6] (the Leuven study) where blood glucose control by IIT decreased mortality and morbidity among surgical ICU patients. The study population included 1548 patients from a single center. The IIT group targeted a blood glucose level of 80–110 mg/dl, whereas the conventional therapy group had a target range of 180–200 mg/dl, with insulin infusion started for blood glucose exceeding 215 mg/dl. The absolute ICU mortality reduction was 3.4% and overall hospital mortality was reduced by one-third, with fewer incidents of organ failure and septicemia. Mortality benefit was greatest for the subgroup of patients whose length of stay in the ICU was more than 5 days.

Without doubt, this landmark study once and forever challenged the past approach to hyperglycemia as the only beneficial adaptation during acute critical illness or trauma, where many factors such as glucogenolysis, catecholamine release, increased gluconeogenesis, peripheral insulin resistance and impaired glucose uptake all play a role in generating stress hyperglycemia.

Recommendations from the Leuven study were internationally endorsed and incorporated into guidelines by 16 professional societies, including the American Diabetes Association, the American Association of Clinical Endocrinologists, and the Surviving Sepsis Campaign. Similar benefits of IIT were demonstrated among 2000 medical, non-surgical ICU patients from the same center in 2006 [7].

However, some recent prospective trials failed to confirm the initial Leuven data, showing conflicting results (no benefit mortality in IIT group, more hypoglycemic episodes) and

ICU = intensive care unit

IIT = intensive insulin therapy

suggesting that the "optimal" target range of blood glucose is unknown at present and seems higher than normoglycemia [8-10]. A recent (2009) meta-analysis of 26 randomized controlled trials [11] with a total of 13,567 patients found that IIT was not associated with overall mortality benefit, except in the surgical patients, but increased the risk of severe hypoglycemia (< 40 mg/dl). The latest systemic review (2011), including 21 trials [12] in different intensive care, perioperative care, myocardial infarction and stroke or brain injury settings, reached the same conclusions.

We would like to mention some of the trials included in these meta-analyses. In two large multicenter European trials [9,10] involving mixed ICU patients, efficacy and safety of IIT (blood glucose target 80–110 mg/dl) was compared to that of conventional therapy, targeting at 140–180 mg/dl in the GLUCONTROL study and 180–200 mg/dl in the VISEP study. Both failed to confirm a beneficial effect of IIT on ICU [9] or 28 day mortality and organ failure [10]. Moreover, these trials were terminated early for safety due to hypoglycemia concerns. The largest multicenter international NICE-SUGAR study [8], with 6104 mixed ICU patients, showed that IIT for glucose control at 81–108 mg/dl increased 90 day mortality compared with conventional glucose control at < 180 mg/dl, without difference in rate of organ failure, LOS and time on mechanical ventilation. Finally, our own trial published in 2007 [13] (n=89) did not show significant benefit of IIT targeting at 110–140 mg/dl when compared with conventional therapy at < 200 mg/dl among mixed ICU patients.

Since glucose targets are a key determinant of safety, intensive insulin therapy with above normoglycemia target range (~140–180 mg/dl) will be safer and more appropriate, while waiting for further results

Although the reasons for these discrepancies among trials remain unclear, there are some explanations for these results. Firstly, the studies were highly heterogeneous, using different methodological and nutritional strategies. In addition, different infusion protocols and routes for insulin administration were used, as well as different sampling sites and techniques for glucose measurement. The practical aspects of intensive glycemic control implementation deserve to be considered.

PROTOCOLS FOR INSULIN INFUSION

According to the recommendations of the American Diabetes Association 2010 [14], a validated intravenous insulin infusion protocol that has demonstrated efficacy and safety in achieving a target glucose range without increasing the risk of severe hypoglycemia is required to control hyperglycemia in critically ill patients. The ideal insulin infusion protocol should a) achieve glycemic control in a reasonable timeframe, b) carry a minimal risk of hypoglycemia, 3) have a low operator error rate, and 4) require minimal nursing time. Apart from that, the most suitable protocol is dynamic and not a sliding-scale [15-17]; it uses the "if-then" rule and relies primarily on rate of change from the prior glucose level rather than solely on the absolute blood glucose value, as well as on the current insulin infusion rate with permitted "off-protocol" adjustments and bolus doses. These are elements of a good protocol that will facilitate safer and more effective insulin administration [15-17]. Unfortunately, there is no consensus about a "standard care" regimen or efficiency, as was well demonstrated in a review of 12 different protocols from several countries [15]. Importantly, one protocol may not fit all patients.

PRACTICAL CONSIDERATIONS

Protocol implementation can be difficult even under close supervision, due not only to a relatively narrow target range (30–40 mg/dl) but also because glucose control is primarily nurse-driven, as nurses, compared to other members of the ICU staff, are significantly more concerned with increased frequency and accuracy of glucose measurements and insulin dose titration necessary to achieve the target blood glucose level safely. Furthermore, results obtained from the Glucontrol study [18] showed that the time nurses devoted to glucose measurements according to protocol was increased by 17%. So, the fear of hypoglycemia and increased work overload may become limiting factors in adopting lower glycemic targets. Thus, the nurse/patient ratio must be adequate to accommodate the protocol requirements.

Another practical problem is the difficulty in achieving target glucose, where failure is common and is associated with increased mortality. In a French study [19], the glycemic control target (90–126 mg/dl) was achieved in less than two-thirds of critically ill patients under intensive insulin strategy.

In recent large trials, such as GLUCONTROL and NICE-SUGAR [8,9] targeted glycemia was not achieved either [Table 1]. Wiener et al. [20] reviewed 29 RCTs and revealed that in 6 trials (21%) the targeted glucose level was not confirmed.

SAFE GLUCOSE CONTROL

The protocol for IIT should be implemented in a safe manner. Recently, there have been growing concerns about hypoglycemia being the major potential danger of this treatment, particularly since it is a preventable event.

All recent studies of tight glucose control have reported increased rates of significant hypoglycemia. Of note, most of these studies defined hypoglycemia as ≤ 40 mg/dl blood glucose concentration and recorded whether any associated symptoms were reported. However, this definition is well

LOS = length of stay

RCT = randomized controlled trial

Table 1. Summary data from RCTs of IIT in the ICU

			Glycemia targeted (mg/dl)		Glycemia achieved (mg/dl)	
Trial	No. of patients	Type of ICU	Intensive glucose control	Conventional glucose control	Intensive glucose control	Conventional glucose control
Glucontrol [16]	1101	Mixed	80–110	140–180	118	144
NICE-SUGAR [8]	6104	Mixed	81–108	144–180	118	145
VISEP [19]	537	Mixed	80–110	180–200	112	151
Leuven 1 [6]	1548	Surgical	80–110	180–200	103	153
Leuven 2 [7]	1200	Medical	80–110	180–200	111	153

Of note, the achieved glycemia reported are the mean morning levels, except for those for the Glucontrol study, which are mean overall blood glucose levels

Adapted from Inzucchi SE, Siegel MD. Glucose control in the ICU – how tight is too tight? *N Engl J Med* 2009; 360: 1346-9. [21]

Table 2. Rate of hypoglycemia (< 40 mg/dl) in RCTs on IIT among surgical/medical ICU patients

		Outcome: No./total no. of patients (%)		
Subgroup	No. of studies	Intensive insulin therapy	Conventional therapy	Relative risk (95% confidence interval)
Very tight control (≤ 110 mg/dl)	11	409/2895 (14.1)	75/2952 (2.5)	5.23 (4.12–6.64)
Moderately tight control (≤ 150 mg/dl)	4	41/380 (10.8)	9/386 (2.3)	4.37 (2.19–8.72)
Overall	15	450/3275 (13.7)	84/3338 (2.5)	5.13 (4.09–6.43)

Of note, the definition of hypoglycemia used in these trials is well below the glucose level that the American Diabetes Association considers as representing hypoglycemia (< 70 mg/dl). All outcome measures were calculated on a per patient basis; for example, a patient with several episodes of hypoglycemia would only count as one occurrence for that outcome.

Adapted from Wiener RS, Wiener DC, Larson RJ. Benefits and risks of tight glucose control in critically ill adults: a meta-analysis. *JAMA* 2008; 300: 933-44. [20]

below the glucose level that the American Diabetes Association considers as representing hypoglycemia (< 70 mg/dl). This strict limitation was used to reveal hypoglycemic events severe enough to have potential clinical relevance.

In the aforementioned meta-analysis [20] that includes 29 published RCTs totaling 8432 patients, in 15 trials the hypoglycemia rate with IIT had increased roughly fivefold, regardless of the ICU setting, and the tighter the glucose control the greater the risk of hypoglycemia [Table 2], without a significant reduction in hospital mortality. In another recent meta-analysis [11] reviewing 26 RCTs totaling 13,567 patients, including our study [13], the range of hypoglycemia (< 40 mg/dl) in the intervention group was between 5.1% and 28.6%. In the large NICE-SUGAR study it was 6.8% with IIT versus 0.5% in the conventional treatment group. Furthermore, two European multicenter trials [9,10] were terminated early due to an increased rate of hypoglycemia in the IIT group (VISEP 17% vs. 4.1%, GLUCONTROL 9.8% vs. 2.7%).

Hospitalization carries several risk factors for hypoglycemia – such as inadequate glucose monitoring, lack of coordination between transportation and nursing, variation from protocol, and concurrent medications (quinolones, epinephrine, beta blockers) [17]; the most important risk factor, however, is cessation of nutritional support during insulin infusion, leading to mistiming of insulin dosage with respect to feeding [22]. Among other predictors of hypoglycemia in a hospital setting, namely, advanced age (> 70 years) and renal and hepatic failure, sepsis was associated with highest risk [23].

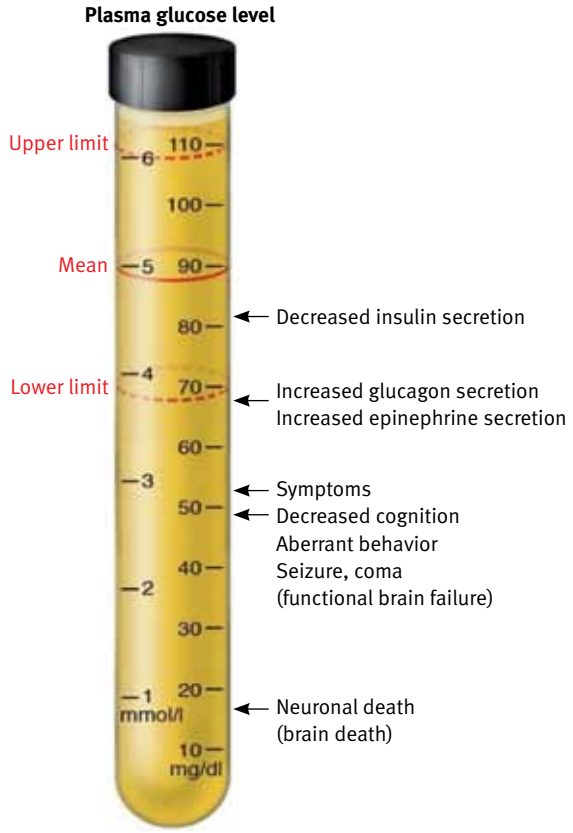
IMPACT OF HYPOGLYCEMIA

Hypoglycemia is not benign in critically ill patients. Even a single episode of severe hypoglycemia (≤ 40 mg/dl) is independently associated with increased mortality, as was found in a series of 5365 medical-surgical ICU patients [24]. In a recently published Australian study [25], even mild (72–81 mg/dl) or moderate (45–71 mg/dl) hypoglycemia is linked to mortality in critically ill patients and the more severe the hypoglycemia the greater the risk of death. Hypoglycemia also occurs spontaneously in hospitalized patients even without a history of diabetes or IIT. Such spontaneous hypoglycemia is much worse than insulin-induced hypoglycemia, with twice the overall mortality rate [23]. However, the total number of hypoglycemic episodes in the published studies on IIT is unknown, probably because clinical signs and symptoms of hypoglycemia, or neuroglycopenia, are usually masked in ICU patients by sedation or critical illness.

Therefore, in clinical practice, where glucose monitoring may be inadequate or less stringent, unrecognized serious adverse effects of hypoglycemia on the heart or brain may result in increased risk of death. Glucose is an obligatory metabolic fuel for the neurons under physiological conditions and the brain cannot synthesize or store glucose as glycogen in astrocytes, so it requires a continuous supply of glucose from the circulation [26]. The rate of blood-to-brain glucose diffusion falls and becomes a limiting factor in brain glucose metabolism [26] when arterial glucose concentrations fall to low levels. The sequence of responses to falling plasma glucose concentrations is illustrated in Figure 1 [26]. Thus, hypoglycemia causes brain fuel deprivation and, as a result, functional brain failure, which is usually corrected by rising plasma glucose concentration. Though rare, profound and prolonged hypoglycemia causes brain death, at least in primates, and oxidative stress through superoxide production is a key event in this cell death process. As was demonstrated by Suh and colleagues [27] in their rodent model, hypoglycemic brain neuronal death is not the result of fuel deprivation per se, but is

To achieve safe glycemic control, a certified, preferably computerized, insulin infusion protocol should be implemented using an accurate measurement technique (arterial samples, arterial gas analyzer)

Figure 1. The sequence of responses to falling plasma glucose concentrations.



Aadapted from Cryer PE. Hypoglycemia, functional brain failure, and brain death. *J Clin Invest* 2007; 117 (4): 868-70. [26]

in fact *increased* by neuronal NADPH oxidase activation during glucose reperfusion. This finding suggests that, at least in profound prolonged hypoglycemia, where risk of neuronal death is higher, plasma glucose levels should be raised carefully but not excessively, avoiding post-treatment hyperglycemia, which can trigger neuronal death. Nonetheless, it would be correct to raise the plasma glucose level to the physiological range (i.e., 70 mg/dl) promptly.

Although there is no clear evidence or proof that therapeutic hyperglycemia is detrimental to recovery, it is seemingly not beneficial in that setting. Of course, future studies of this topic are necessary.

ACCURATE BLOOD GLUCOSE MEASUREMENT

Since treatment decisions in IIT protocols depend exclusively on blood glucose values, accurate blood glucose measurement is crucial for safe insulin dose adjustment necessary to achieve the desired blood glucose level and avoid hypoglycemia. One of the main strategies to increase acceptance of intensive insulin strategy in the ICU may be the embedding of highly reliable point-of-care testing devices. There is growing concern regarding low accuracy of glucose meter measurements and central remote laboratory turnaround because of their lack of safety and unacceptable timing delay. Glucometers are usable, although they were originally developed for out-of-hospital glucose control, not for IV insulin dose titration in critically ill patients in the ICU, despite their "acceptable performance" [28]. Allowable error range for the central laboratory is 10%; for glucometers it is 20%, as permitted by the United States Food and Drug Administration [28], thus they are less precise than central laboratory or blood gas analyzers and with these methods can demonstrate large mean differences [29,30].

So, at present, the most accurate and suitable method in the ICU setting for blood glucose measurement is the arterial blood gas analyzer in whole arterial blood (autocalibration to plasma glucose x 1.11). Furthermore, the different methods used by presently available glucometers (glucoseoxidase, -hexokinase, -dehydrogenase) may be affected by site and source of glucose sampling, as well as by common conditions in critically ill patients – namely, low PO_2, poor perfusion, hypotension, low/high hematocrit, vasopressors, presence of non-glucose sugars [17,31]. The samples obtained from whole blood (arterial or venous) for glucometers differ less from the laboratory reference than that obtained from capillary blood or subcutaneous interstitial fluid by finger stick [32]. Another variable is that, under physiological conditions, glucose concentration determined from arterial sites generally exceeds that of capillary sites, which, in turn, is greater than venous sites, although these differences are minimal. Taken together, capillary samples may be artificially lower or higher than arterial/vein samples [17,28,32].

According to the level of accuracy, we would put the different methods and sample sites in the following order: Central laboratory > ABG analyzer > arterial blood sample by glucometer > venous blood sample by glucometer > capillary blood sample by glucometer. In addition, the American Diabetic Association [33] and the National Academy of Clinical Biochemistry recommend the central laboratory method, not the glucose meter, for the diagnosis of diabetes. If a device is not to be used for diagnosis, which depends on a single cutoff glucose concentration, how can it be used for making an intravenous insulin dose decision based on precise cutoff values?

Finally, it should be noted that inaccurate blood glucose measurements may be a possible explanation for conflicting results in some of the studies where different methods and sample sites for glucose measurements were used [6,8,28,29]. In conclusion, inaccurate glucometer values will lead to insulin dosing errors, and, as a result, to large blood glucose fluctuations and undetected hypo/hyperglycemia.

ABG = arterial blood gas

BLOOD GLUCOSE VARIABILITY

Accumulating data suggest a role for blood glucose variability as a strong independent predictor of ICU and hospital mortality [34]. A recently published study (abstract) from Saudi Arabia [35] on 523 patients in a surgical ICU found that mortality in a high variability group was more than twofold higher than in a low variability group, especially in an elderly diabetic population ($P < 0.001$).

Furthermore, high mean glucose values combined with high glucose variability is associated with highest ICU mortality, while low glucose variability seemed protective, even when mean glucose levels remained elevated [36]. In other words, the variability in blood glucose may be more important than the actual blood glucose concentration.

These wide fluctuations of glucose level with IIT should be minimized to improve the outcomes of our patients. The potential solution lies in advanced technology for continuous glucose monitoring systems and computerized protocols for IIT, allowing for rapid detection and correction of glucose changes.

FUTURE DEVELOPMENT

Preliminary data report that implementation of computerized protocols for insulin administration has been increasing. In general, applying information technology is intended to help nurses adhere to IIT. These computer-assisted protocols are easer to use than nurse-based ones and have at least the same efficiency and a lower hypoglycemia rate with less staff workload [37].

The development and clinical implementation of continuous glucose monitoring technology and the closed-loop fully/semi-automated system, coupled with the feedback algorithm based on frequent and accurate blood glucose measurements obtained by an in vivo glucose sensor, are the key to safe and effective glycemic control in real time [38]. An artificial pancreas, which could become a reality in the future, carries great promise for enabling in-hospital glucose control due to elimination of the risk of severe hypoglycemia and, consequently, may improve clinical outcome, reduce length of stay and lower the costs. The combination of reliable continuous glucose measurements with a microprocessor system would reduce the effects of peripheral hypoperfusion and other confounding variables that interfere with glucometer monitoring. One of the first steps on this path is the development of a reliable glucose sensor. There are various techniques for continuous glucose monitoring, namely, subcutaneous electrode or catheter for sample taking from interstitial fluid, intravascular sensor, and non-invasive optical probe. Generally, three major types of closed-loop systems applying these techniques are currently recognized [38]: first is the subcutaneous sensing and subcutaneous delivery system, the second is the intravenous or subcutaneous sensing and intraperitoneal delivery system, and the third is the intravenous glucose sensor and intravenous delivery system. The third type seems more suitable for the acute critically ill patient, due to its more accurate blood glucose sampling and more predictable pharmacokinetics, allowing for quick response to a rapidly changing glucose level with smaller insulin doses, as well as automated blood sample aspiration, flush, and recalibration without blood loss [39]. The unreliability of the subcutaneous sensor and unpredictable absorption of subcutaneous insulin in critically ill patients make this approach an inappropriate option for intensive care environments [17,39]. At present, despite the advantages of these advanced technologies, their practical implementation is still limited.

DISCUSSION

A synthesis of evidence from different trials shows that IIT does not improve health outcomes among critically ill patients, except for a small reduction of septicemia in surgical patients, but it is associated with substantial risk for severe hypoglycemia, regardless of the ICU setting and targeted glucose goal [11,12,20]. Initial benefits in the Leuven study [6] have not been subsequently realized despite attempts to do so. Furthermore, IIT is difficult to implement safely. Accumulated data suggest that under real-life ICU circumstances, very tight glycemic control (80–110 mg/dl) may be detrimental due to increased risk of overt hypoglycemia, unless we apply it under conditions that are close to the Leuven studies [6,7]: highly trained and adequately staffed team, accurate glucose measurements, and sufficient sampling frequency with mostly parenteral high energy intake strategy. If these conditions cannot be met, it would appear unsafe to apply routinely strict glycemic control in all categories of critically ill patients, especially in ICUs that are not equipped and trained to adequately measure/monitor of blood glucose.

In this situation, glycemic control with an above normoglycemia target (~140–180 mg/dl) seems to be the more appropriate option. Despite the benefits of achieving more moderate blood glucose targets, which have not been established, less strict glucose control is associated with a lower rate of hypoglycemia [12,13,20]; therefore, it is imperative that such control minimize harm. Put differently, glucose targets are a key determinant of safety, although it probably depends on multiple factors, such as protocol characteristics, specific patient population, and local institutional and provider resources [12,15,17].

On the other hand, the association of hyperglycemia with adverse outcomes and an increased risk for infection has caused many institutions to continue IIT, but less aggressively. Surprisingly, many of the ICUs have not updated their IIT policy since the results of large multicenter randomized trials were published in 2008–2009 [8-10], which did not find a survival benefit with strict glycemic control. A recently (2011) published survey of all British adult ICUs revealed that 46% of the units had changed their IIT policy in response to

new evidence with higher target limits and a wider target range, whereas 54% had not updated their glycemic control practice [40]. This finding may reflect continued interest and confidence in IIT because of potential complications of hyperglycemia. We revised our glycemic control practice from the previous target of 110–140 mg/dl to 140–180 mg/dl more than one year ago, and it was easier to adopt higher limits and a wider glycemic range.

Finally, the health benefits of moderate glucose level targets (140–200 mg/dl) should be examined. Further multicenter trials including a larger number of patients are necessary to define the optimal target range of blood glucose for IIT with the best benefit-to-risk ratio. However, highly accurate glucose measurements and insulin administration protocols among institutions should be standardized to avoid heterogeneity in results.

In our view, the main question is whether glycemic regulation in the ICU can be effective and safe at the same time? Is it possible to find a right balance between real risk and potential benefit of intensive insulin strategy? The answer lies, probably, in respecting the concept of *primum non nocere* (First, do no harm). Although this is one of the cornerstones of medical practice, it is often forgotten. Currently, clear evidence for and against tight glucose control in the ICU is still lacking. There are important methodological differences among studies, possibly explaining different outcomes, which do not permit us to make definitive conclusions. Therefore, until the results of further studies are available, we absolutely agree with American researcher Phillip E. Cryer, who wrote: "…until a favorable benefit-risk relationship is established in rigorous clinical trials …euglycemia is not an appropriate goal during critical illness in the routine clinical setting with current treatment methods."

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References

1. Christiansen C, Toft P, Jørgensen HS, Andersen SK, Tønnesen E. Hyperglycaemia and mortality in critically ill patients. A prospective study. *Intensive Care Med* 2004; 30: 1685-8.
2. Krinsley JS. Association between hyperglycemia and increased hospital mortality in a heterogeneous population of critically ill patients. *Mayo Clin Proc* 2003; 78: 1471-8.
3. Meyfroidt G, Keenan DM, Wang X, Wouters PJ, Veldhuis JD, Van den Berghe G. Dynamic characteristics of blood glucose time series during the course of critical illness: effects of intensive insulin therapy and relative association with mortality. *Crit Care Med* 2010; 38 (4): 1021-9.
4. Kreutziger J, Wenzel V, Kurz A, Constantinescu MA. Admission blood glucose is an independent predictive factor for hospital mortality in polytraumatised patients. *Intensive Care Med* 2009; 35: 1234-9.
5. Sutcliffe AJ. Hyperglycemia in trauma: Critical Care Section D. Traumatic brain injury: critical care management. In: Wilson WC, Grande CM, Hoyt DB, eds. Trauma Critical Care. Vol 2. New York: Informa Healthcare, 2007: 206-7
6. Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med* 2001; 345: 1359-67.
7. Van den Berghe G, Wilmer A, Hermans G, et al. Intensive insulin therapy in the medical ICU. *N Engl J Med* 2006; 354: 449-61.
8. Finfer S, Chittock DR, Su SY, et al., for NICE-SUGAR Study Investigators. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med* 2009; 360: 1283-97.
9. Devos P, Preiser JC, Melot C. Impact of tight glucose control by intensive insulin therapy on ICU mortality and the rate of hypoglycemia: final results of the Glucontrol study. *Intensive Care Med* 2007; 33 (Suppl 2): S189.
10. Brunkhorst FM, Engel C, Bloos F, et al., for. German Competence Network Sepsis (SepNet). Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med* 2008; 358: 125-39.
11. 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: 821-7.
12. Kansagara D, Fu R, Freeman M, Wolf F, Helfand M. Intensive insulin therapy in hospitalized patients: a systematic review. *Ann Intern Med* 2011; 154: 268-82.
13. Farah R, Samokhvalov A, Zviebel F, Makhoul N. Insulin therapy of hyperglycemia in intensive care. *IMAJ Isr Med Assoc J* 2007; 9: 140-2.
14. Executive Summary: Standards of Medical Care in Diabetes – 2010. *Diabetes Care* 2010; 33: S4-10; doi:10.2337/dc10-S004.
15. Wilson M, Weinreb J, Hoo GW. Intensive insulin therapy in critical care: a review of 12 protocols. *Diabetes Care* 2007; 30: 1005-11.
16. Goldberg PA, Siegel MD, Shervin RS, et al. Implementation of a safe and effective insulin infusion protocol in a medical intensive care unit. *Diabetes Care* 2004; 27: 461-7.
17. D'Hondt NJ. Continuous intravenous insulin: ready for prime time. *Diabetes Spectrum* 2008; 21 (4): 255-61.
18. Perreaux J, Devos P, Prieser JC, et al., for Glucontrol Steering Committee. Impact of the implementation of tight glucose control by intensive insulin therapy on the nursing workload. Data from the Glucontrol study [Abstract]. *Intensive Care Med* 2007; 33 (S2): S5.
19. Lacherade JC, Jabre P, Bastuji-Garin S, et al. Failure to achieve glycemic control despite intensive insulin therapy in a medical ICU: incidence and influence on ICU mortality. *Intensive Care Med* 2007; 33: 814-21.
20. Wiener RS, Wiener DC, Larson RJ. Benefits and risks of tight glucose control in critically ill adults: a meta-analysis. *JAMA* 2008; 300: 933-44.
21. Inzucchi SE, Siegel MD. Glucose control in the ICU – how tight is too tight? *N Engl J Med* 2009; 360: 1346-9.
22. Elia M, De Silva A. Tight glucose control in intensive care units: an update with an emphasis on nutritional issues. *Curr Opin Clin Nutr Metab Care* 2008; 11: 465-70.
23. Kagansky N, Levy S, Rimon E, et al. Hypoglycemia as a predictor of mortality in hospitalized elderly patients *Arch Intern Med* 2003; 163: 1825-9.
24. Krinsley JS, Grover A. Severe hypoglycemia in critically ill patients: risk factors and outcomes. *Crit Care Med* 2007; 35: 2262-7.
25. Egi M, Bellomo R, Stachovsky E, et al. Hypoglycemia and outcome in critically ill patients. *Mayo Clin Proc* 2010; 85: 215-24.
26. Cryer PE. Hypoglycemia, functional brain failure, and brain death. *J Clin Invest* 2007; 117 (4): 868-70.
27. Suh SW, Gum ET, Hamby AM, et al. Hypoglycemic neuronal death is triggered by glucose reperfusion and activation of neuronal NADPH oxidase. *J Clin Invest* 2007; 117: 910-18.
28. Scott MG, Bruns DE, Boyd JC, Sacks DB. Tight glucose control in the intensive care unit: are glucose meters up to the task? *Clin Chem* 2009; 55: 18-20.
29. Sacks DB. Intensive glucose control in the ICU: is SUGAR NICE? *Nat Rev Endocrinol* 2009; 5 (9): 473-4.
30. Vlasselaers D, Van Herp T, Milants I, et al. Blood glucose measurements in arterial blood of intensive care unit patients submitted to tight glycemic control: agreement between bedside tests. *J Diabetes Sci Technol* 2008; 2 (6): 932-8.
31. King DA, Ericson RP, Todd NW. Overestimation by a hand-held glucometer of blood glucose level due to icodextrin. *IMAJ Isr Med Assoc J* 2010; 12: 314-15.

32. Desachy A, Vuagnat AC, Ghazali AD, et al. Accuracy of bedside glucometry in critically ill patients: influence of clinical characteristics and perfusion index. *Mayo Clin Proc* 2008; 83 (4): 400-5.

33. Diagnosis and classification of Diabetes mellitus – 2010. *Diabetes Care* 2010; 33: S67.

34. Krinsley JS. Glycemic variability: a strong independent predictor of mortality in critically ill patients. *Crit Care Med* 2008; 36 (11): 3008-13.

35. Al-Dorzi HM, Tamim HM, Arabi YM. Glycemic variability: predictors and relationship to outcomes in critically ill patients. American Thoracic Society 2008 International Conference: Abstract A767. Presented May 20, 2008.

36. Hermanides J, Vriesendorp TM, Bosman RJ, et al. Glucose variability is associated with intensive care unit mortality. *Crit Care Med* 2010; 38 (3): 838-4.

37. Cordingley JJ, Vlasselaers D, Dormand NC, et al. Intensive insulin therapy: enhanced model predictive control algorithm versus standard care. I*ntensive Care Med* 2009; 35 (1): 123-8.

38. Hovorka R. The future of continuous glucose monitoring: closed loop. *Curr Diabetes Rev* 2008; 4 (3): 269-79.

39. Joseph JI, Hipszer B, Mraovic B, et al. Clinical need for continuous glucose monitoring in the hospital. *J Diabetes Sci Technol* 2009; 3 (6): 1309-18.

40. Paddle JJ, Eve RL, Sharpe AK. Changing practice with changing research: results of two UK national surveys of intensive insulin therapy in intensive care patients *Anaesthesia* 2011; 66: 92-6.