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HOSPITAL MANAGEMENT OF DIABETES (G UMPIERREZ, SECTION EDITOR)

Diabetes and Hyperglycemia in the Critical Care Setting: Has the Evidence for Glycemic Control Vanished? (Or … Is Going Away?)

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Abstract Hyperglycemia is associated with increased mortality and other complications amongst hospitalized patients. However, the studies of tight glycemic control in a range of critical illness settings, including intensive care, acute myocardial infarction, and stroke, have produced inconsistent and divergent results. We examine some of the factors that may have contributed to the differing results, and their implications for targeting tight glucose control in critical illness. With these in mind, most clinical guidelines now recommend moderate glucose control with an upper glucose target of <10 mmol/L (180 mg/dL) in critical illness while avoiding hypoglycemia.

Keywords Hyperglycemia · Diabetes · Glucose · Critical illness · Hospital · Intensive care · Glycemic control · Critical care setting

Introduction

The last 20 years has seen considerable interest in the area of glucose control in critical illness. Trials in the 1990s and early 2000s brought a wave of enthusiasm for tight glucose control, and this was reflected in clinical management guidelines. Subsequent studies however, have produced mixed results. Glucose control in critical illness remains a hotly debated topic, being the subject of numerous reviews, meta-analyses and commentaries in recent years. Adopting a broad approach to the term "critical illness" to include not just patients in intensive care units (ICU), but also those with acute myocardial infarction (AMI) and stroke, we will examine the key trials, their implications, and influence on this field.

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The Association between Hyperglycemia and Adverse Hospital Outcomes

The relationship between hyperglycemia and adverse hospital outcomes including mortality, infection, poor wound healing, cardiac complications, and increased length of hospital stay, is well established. There are data from a variety of settings including intensive care [1, 2], myocardial infarction [3–6], stroke [7, 8], trauma [9], cardiac surgery [10], total parenteral nutrition [11], emergency ward [12], and general hospital wards [13]. There is a dose response, with higher glucose levels being associated with greater risk. A "j-curve" of risk has also been described, with hypoglycemia also being associated with increased mortality in ICU [2], emergency [12], and AMI [5, 6].

The question has been whether hyperglycemia contributes to increased mortality or is merely a marker of increased severity of illness. While there is clear evidence that critical illness activates stress hormones and inflammatory processes resulting in insulin resistance, increased hepatic gluconeogenesis, and hyperglycemia [14], there are clinical, animal, and in vitro studies, which support a pathogenetic role of acute hyperglycemia as well. Examples include impairment of leucocyte function, increased rates of infection [15–19], increased oxidative stress [20], C-reactive protein and other inflammatory cytokines [20, 21], and hypercoagulability [22]. High glucose levels have been associated with increased myocardial damage and cell apoptosis during ischemia [23, 24] and with the size of stroke and level of salvage of the ischemic penumbra [25].

However, randomized controlled trials (RCTs) of tight glycemic control have produced inconsistent results, so the benefit of treatment of hyperglycemia in critical illness remains disputed. We will review some of the important trials below (Table 1).

Key Trials of Tight Glycemic Control in Intensive Care

Leuven Surgical ICU Study

This study included 1548 patients admitted to a single surgical ICU in Belgium [26]; 13 % had known diabetes; most had undergone cardiac surgery (63 %). Patients were randomized to intensive insulin therapy, with an insulin infusion if blood glucose (BG) exceeded 6.1 mmol/L (110 mg/dL) targeting the "normal range" of 4.4–6.1 mmol/L (80–110 mg/dL), or conventional therapy, where an insulin infusion was commenced if the BG was >11.9 mmol/L (215 mg/dL), targeting 10–11.1 mmol/L (180–200 mg/dL). All patients received intravenous glucose (200–300 g), and the majority parenteral nutrition. Blood glucose was monitored 1–4 hourly, on arterial samples, with a blood gas analyzer.

The intervention arm achieved a lower mean morning BG (5.8 vs 8.5 mmol/L, $P<0.001$). Intensive insulin therapy reduced ICU and hospital mortality (4.6 % vs 8 %, $P<0.04$ and 7.2 % vs 10.9 %, $P=0.01$, respectively). There was also a reduction in septicemia by 46 %, need for dialysis or hemofiltration by 41 %, prolonged ventilatory support by 37 %, critical illness polyneuropathy by 44 %, and prolonged ICU length of stay by 27 %. Multivariate analysis indicated that it was glucose control, rather than insulin therapy, which was related to the reduction in mortality [27]. Hypoglycemia, defined as a BG ≤2.2 mmol/L (40 mg/dL) occurred in 5 % of intensive arm subjects and 1 % of those in the control arm.

The publication of this study in 2001 led to the adoption of protocols aiming for tight glycemic control in many ICUs, and guidelines recommending these targets.

Leuven Medical ICU Study

Following these results, a similar study was conducted at the Leuven Medical ICU, where 1200 patients were randomized to the same treatment arms and glucose targets [28]. However, no difference was seen in hospital mortality (40 % vs 37.3 %, hazard ratio 0.93; 95 % CI 0.84–1.06, $P=0.31$), though amongst those who stayed ≥3 days in ICU, mortality was lower with intensive insulin therapy. Conversely, mortality was higher in those that stayed less than 3 days in ICU. Morbidity was improved, including reduced acute renal failure, prolonged mechanical ventilation, and length of stay in ICU and hospital.

Hypoglycemia occurred in 19 % of the intervention group vs 3 % of controls (HR 5.94; 95 % CI 3.70–9.54, $P<0.001$).

Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation (NICE-SUGAR) Study

RCTs subsequent to the Leuven studies have not replicated their findings in any adult ICU setting [29–34, 35•]. High rates of hypoglycemia have been problematic, with 1 trial being terminated early because of this [29].

The largest of these trials was the NICE-SUGAR Study, a multinational RCT conducted in mixed medical/surgical ICUs [34]. Six thousand one hundred and four subjects with an anticipated ICU stay of 3 days or more were randomized to an intensive glucose target of 4.5–6.0 mmol/L (81–100 mg/dL) or control target of 8–10 mmol/L (144–180 mg/dL).

The primary end point of 90 day mortality was unexpectedly increased with tight control (27.5 vs 24.9 %, odds ratio 1.14, 95 % CI 1.02–1.28, $P=0.02$). The results were not different for surgical and nonsurgical patients, or patients with and without diabetes. There was no difference in any secondary outcome. There was a higher incidence of death from cardiovascular causes in the intensive group. Both severe (BG≤2.2 mmol/L) and moderate hypoglycemia (2.3–3.9 mmol/L) were increased (6.8 % vs 0.5 %, $P<0.001$ and 72.4 % vs 15.8 %, respectively) [35•].

Key Trials of Tight Glycemic Control in Myocardial Infarction

Most cardiac trials of insulin therapy in AMI have focused on the delivery of glucose-insulin-potassium solutions rather than glucose control [36]. There are only 3 large RCTs with primarily a glycemia focus.

Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI) Study

DIGAMI was the first RCT to examine the impact of glycemic control in AMI. Subjects with BG >11 mmol/L (198 mg/dL) were randomized to a combined intervention of insulin infusion for at least 24 hours (target BG 7–10 mmol/L [126–180 mg/dL]) followed by at least 3 months of intensive subcutaneous insulin therapy, or to usual care [37].

After 24 hours, BG was lower in the intervention group (9.6±3.3 vs 11.7±4.1, $P<0.0001$). At 3 months, HbA1c was lower in the intervention group (7.0±1.6 vs 7.5±1.8 %, $P<0.001$). Mortality was similar at discharge and at 3 months but was reduced at 12 months (18.6 % vs 26.1 %, $P=0.0273$). This survival benefit persisted at 3.5 years follow-up [38].

While these results demonstrated the benefits of glycemic control after AMI, it remained unclear to what extent this resulted from improved inpatient control, as opposed to postdischarge care.

Table 1 Key randomized controlled trials of glucose control in critical illness

	Subjects	Intervention and glucose target (mmol/L)	Achieved glucose (mmol/L)	Mortality	Hypoglycemia (mmol/L)	Blood source for glucose monitoring	Glucose measurement
Cardiac Setting							
DIGAMI, Malmberg, 1995 [37]	620	IG: 7–10 CG: no target	24 h BGL: IG: 9.6 CG: 11.7 ($P<0.0001$)	No difference 90 d but reduced 12 mo mortality (18.6 % vs 26.1 %, $P=0.0273$)	Defined <4.0 15 % vs 0 %, $P<0.0001$	Capillary	Glucometer
DIGAMI-2, Malmberg, 2005 [39]	1253	IGs: 7–10 Control: no target	24 h BGL: Group 1&2: 9.1 Group 3: 10 ($P=0.0001$)	No difference 2 yr mortality (23.4 % vs 22.6 % vs 19.3 %)	Defined <3.0 12 % vs 9.6 % vs 1 %	Capillary	Glucometer
HI-5, Cheung, 2006 [40]	240	IG: 4–10 CG: <16	24 h BGL: IC: 8.3 CG: 9 (P=NS)	No difference 3 or 6 mo mortality	Defined <3.5 7 % vs 0.9 %, $P=0.02$	Capillary	Glucometer
Stroke							
GIST-UK, Gray, 2007 [41]	933	IG:4–7 CG: no target	IG: BGL 0.57 lower than CG ($P<0.001$)	No difference 90 d mortality	Defined <4 IG: 41.2 %	Capillary	Glucometer
QASC, Middleton, 2011 [42•]	1126	IG: 4–8 if diabetic and BGL≥11 or nondiabetic and BG≥16 CG: No target	IG: 6.8 CG: 7.0 $P=0.02$	Reduced mortality or dependency (42 % vs 58 %, $P=0.002$)		Capillary	Glucometer
ICU							
Leuven Surgery, van den Berghe, 2001 [26]	1548	IG: 4.4–6.1 CG: 10–11.1	Morning BG IG: 5.7 CG: 8.5 ($P<0.001$)	Reduced mortality (4.6 % vs 8 %, $P<0.04$)	Defined <2.2 5 % vs 1 %	Arterial	Blood gas analyzer
Leuven Medicine, van den Berghe, 2006 [28]	1200	IG: 4.4–6.1 CG: 10–11.1	Morning BG IG: 5.8 CG: 8.5 ($P<0.001$)	No difference hospital mortality (40 % vs 37.35 %, $P=0.33$)	Defined <2.2 19 % vs 3 %	Arterial	Blood gas analyzer
NICE-SUGAR, 2008 [34]	6104	IG: 4.5–6.0 CG: 8–10	Morning BG IG: 6.6 CG: 8.1 ($P<0.001$) Time-weighted BG IG: 6.4±1.0 CG: 8.0±1.3 ($P<0.001$)	Increased 90 d mortality (27.5 % vs 24.9 %, $P=0.02$)	Defined ≤2.2 6.8 % vs 0.5 %, $P<0.001$	Mostly arterial, possibly some capillary	Blood gas analyzer, laboratory, or glucometer

DIGAMI-2

DIGAMI 2 was designed to examine the treatment effect of the 2 aspects of DIGAMI separately: acute glucose control and long-term subcutaneous insulin. One thousand two hundred and fifty-three patients were randomized to 3 groups: insulin infusion followed by intensive subcutaneous insulin therapy after discharge, insulin infusion followed by usual care, and usual care only [39].

Baseline HbA1c was 7.2 %–7.3 % across groups; notably better than DIGAMI. Glucose was only modestly lower after 24 hours in the insulin infusion groups (9.1 mmol/L each), compared with usual care (10.0 mmol/L). At discharge less than half of group 1 patients continued to receive multidose insulin injections, and long-term glucose targets were not achieved. There was no significant difference in mortality or morbidity between the 3 groups.

Hyperglycemia: Intensive Insulin Infusion in Infarction (HI-5) Study

The HI-5 study was designed to test the impact of glycemic control using insulin infusion therapy in the peri-infarct setting. 240 subjects with diabetes (48 %) or BG ≥7.8 mmol/L and suspected AMI were randomized to an insulin/dextrose infusion for 24 hours postadmission (target 4.0–10 mmol/L), or routine care [40]. Insulin titration was based on the initiative of the attending nurse, with no specific algorithm.

At 24 hours, there was no statistical difference in BG between groups (8.3±2.2 and 9.0±2.8 mmol/L). Mortality at hospital discharge, 3 and 6 months were similar. There was a lower incidence of cardiac failure and re-infarction within 3 months in the intervention group. Post hoc analysis revealed those with BG <8 mmol/L at 24 hours had lower mortality than those with BG ≥8 mmol/L. Hypoglycemia (BG <3.5 mmol/L) occurred in 7 % of the intervention group and 0.9 % of the control group ($P=0.02$), with none of the episodes being symptomatic.

With no BG difference achieved, the hypothesis that tight glycemic control in the peri-infarct setting might reduce mortality was not adequately tested.

Key Trials of Tight Glycemic Control in Stroke

While there are a number of RCTs of glucose control in acute stroke, the 2 most significant are the GIST-UK and QASC Trials.

UK Glucose Insulin in Stroke (GIST-UK) Trial

GIST-UK recruited 933 subjects with BG 6.0– 17.0 mmol/L and within 24 hours of stroke onset and randomized them to either insulin/glucose/potassium infusion therapy (target 4.5–7.0 mmol/L) or saline infusion for 24 hours [41].

The trial was stopped early due to slow recruitment and was therefore underpowered. Most patients had only mild hyperglycemia (median BG 7.6 mmol/L) on admission. BG fell in both groups at 24 hours, but was slightly lower in the intervention group (0.57 mmol/L difference, $P<0.001$). There was no difference in 90 day mortality or morbidity between groups. Persistent hypoglycemia (<4 mmol/L) >30 minutes requiring rescue treatment occurred in 15.7 % of the intervention group.

Quality in Acute Stroke Care (QASC) Study

In the QASC trial, 19 acute stroke units (ASU) were enrolled in a cluster randomized trial [42•]. The intervention comprised a package of nursing-based education and protocols directed at fever, hyperglycemia, and dysphagia management. Treatment for hyperglycemia involved an insulin infusion if BG >11 mmol/L (in patients with diabetes) or BG >16 mmol/L if not. Control ASUs received an abridged version of the guidelines only. The primary outcome was a composite of death and dependency.

At 90 days postdischarge, fewer patients at the intervention hospitals were dead or dependent (42 % vs 58 %, $P=0.002$). The mean BG was only slightly lower amongst the intervention subjects (6.8 vs 7.0 mmol/L, adjusted absolute reduction 0.54 mmol/L, 95 % CI 0.08–1.01, $P=0.02$). While this suggests that even modest glucose lowering may be beneficial, the multifaceted intervention design did not enable this to be determined with certainty.

Trials of Tight Glycemic Control in General Wards

RABBIT2-Surgery Study

The RABBIT2-Surgery Study did not include critically ill patients, but it is instructive to examine as it provides evidence of benefit of glucose control in the hospital setting. This study was primarily designed to compare 2 protocols for achieving tight glycemic control in diabetic patients admitted for surgery [43•]. 211 diabetic subjects with an admission BG of 7.8–22.2 mmol/L (140–400 mg/dL) were randomized to receive basal bolus and correction insulin or sliding scale insulin to achieve a target fasting and premeal BG of 5.6–7.8 mmol/L (100–140 mg/dL) for the duration of their admission.

Basal bolus insulin achieved better glycemic control with a mean glucose during admission of 8.7±1.8 mmol/L vs 9.8±2.4 mmol/L ($P<0.001$), and a higher percent of readings in the target range (51.8 % vs 31.7 %, $P<0.001$). There was a reduction in postoperative complications (composite of wound infection, pneumonia, bacteremia, respiratory failure, and acute renal failure), occurring in 9 % patients in the basal

bolus group compared with 24 % in the sliding scale group ($P=0.003$). The difference in wound infections was also close to significance ($P=0.05$).

Hypoglycemia (<3.9 mmol/L) was more common with basal bolus insulin (23.1 vs 4.7 %, $P<0.001$), though rarely severe (BG ≤2.2 mmol/L, 3.8 v 0 %, $P=0.053$).

The RABBIT2-Surgery study effectively tested 2 different levels of glycemic control, demonstrating that surgical complications are less likely when the patient has a mean pre-meal BG of 8.7 mmol/L.

Meta-Analyses of Tight Glycemic Control in Critical Illness

Several meta-analyses have attempted to synthesize the evidence for glycemic control in ICU and hospital settings [44–51] (Table 2). None have found a benefit of tight control on mortality. Three meta-analyses suggest a benefit in surgical patients [44–46], and 3 have found a reduction in infection overall or amongst surgical patients [45–47]. Of the 3 meta-analyses on neurologic patients [47–49], 2 suggest some benefit of glucose control on neurologic outcome [47, 48], even without inclusion of the recent QASC Study. Although the majority of the meta-analyses found no evidence of heterogeneity across the studies, factors such as method of glucose testing were not analyzed. In all settings, intensive control increases hypoglycemia, by 3– 25 times compared with conventional control.

Why Have There Been Such Disparate Results in the Trials?

Much has been written in the last 3 years comparing the Leuven Trials with the NICE-SUGAR Trial. Van den Berghe has pointed out that the control group in the NICE-SUGAR study had a lower target range (8–10 mmol/L) than in the Leuven Studies (10–11 mmol/L) hence the likelihood of observing a benefit was smaller [52]. Furthermore, <50 % of patients in the intensive group of NICE-SUGAR were on average, within the target range. Questions about the accuracy of glucose testing, which would affect attainment of glucose targets and occurrence of hypoglycemia, have been raised (see below). There are also concerns as to whether there was adequate testing for and management of hypokalemia arising from insulin therapy. There was a more aggressive feeding regimen in the Leuven study, which possibly benefited from the co-treatment with insulin. Finally, the Leuven study was conducted in a single experienced center, while NICE-SUGAR involved 41 centers. Lack of experience and unfamiliarity with protocols in busy ICUs may affect a unit's ability to safely target tight glycemic control. Given these disparities, many have not discounted the benefits of tight glycemic control in ICU.

In the area of AMI, there are several factors which may have contributed to the failure of the more recent trials to demonstrate better outcomes with tight control. These include the failure to achieve a sufficient glycemic difference between intervention and control arms, in part due to the relatively low glucose levels in the control subjects of HI-5 and DIGAMI-2, which were even lower than the intervention subjects in DIGAMI. Another major factor is the dramatic fall in mortality in the years since DIGAMI, with the advent of rapid angioplasty, aspirin, beta-blockade, and statin therapy (26.1 % 1 year mortality in the control group of DIGAMI compared with 8.9 % in HI-5). This does not mean that glucose control is not important, but its relative mortality impact is smaller, and its effect becomes more difficult to demonstrate [53].

Improving Safety of Tight Glucose Control

Prevention and Recognition of Hypoglycemia

The major concern with tight glucose control is the risk of hypoglycemia. A post-hoc analysis of the NICE-SUGAR Study found an independent and dose-dependent effect of hypoglycemia on mortality, irrespective of underlying diabetes [35•], and there are other observational data that low glucose is associated with increased ICU mortality [54]. While these data do not prove causality, there are nonetheless obvious and established reasons for avoiding hypoglycemia, not least that the brain relies on glucose as an obligate fuel source and this is an insulin-independent process [55].

The cardiac and stroke studies have reported rates of hypoglycemia of up to 15 %, but very few of these cases were of a severity to the same level as the ICU studies. Hypoglycemia therefore has predominantly been an ICU issue. In fact, the true incidence of hypoglycemia may be considerably higher than what has been reported, as detection in sedated ICU patients (unlike coronary care patients) relies purely on glucose testing. For the same reason, hypoglycemia is more likely to be severe amongst ICU patients.

When aiming for tight glycemic control with insulin infusion, frequent testing is mandatory. Both the NICE-SUGAR and Leuven protocols allowed for 2 hourly testing when patients were in the target range (average tested 2½ hourly in NICE-SUGAR). This may result in delay in detection of hypoglycemia, particularly in unstable patients with frequent changes in medication and nutrition delivery. Even in most general wards, patients on insulin-glucose infusions with more liberal targets would receive hourly testing. One tool which shows early promise to facilitate the early detection of hypoglycemia is real-time continuous glucose monitoring (RT-CGMS). This has been demonstrated to reduce the rate of severe hypoglycemia in the ICU setting [56]. Although RT-CGMS is not common practice or recommended in any

Table 2 Meta-analyses of tight glycemic control in critical illness since 2009

	Primary analysis	Studies analyzed	Mortality	Other analyses	Hypoglycemia	Conclusions re tight glucose control
Griesdale et al., 2009 [44]	ICU mortality	26	No difference, RR 0.93 (0.83–1.04)	Reduced surgical ICU mortality	Increased, RR 6.0 (4.5–8.0)	No difference in mortality overall but possible benefit in surgical ICU setting.
Marik et al., 2010 [50]	ICU mortality	7	No difference, OR 0.95 (0.87–1.05)	No difference in infections or dialysis	Increased, RR 7.7 (6–9.9)	No evidence for tight glycemic control in ICU patients who are fed to guidelines
Kansagara et al., 2011 [51]	Hospital mortality, including ICU, AMI, and stroke	21	No difference, RR 1.00 (0.94–1.07)	No difference infections, LOS, dialysis. Diabetes: no difference.	Increased, RR 6.0 (4.06–8.87)	No difference in overall outcome across hospital settings.
Ling et al., 2012 [45]	ICU mortality	22	No difference	Mixed ICU: increased mortality. Surgical ICU: reduced infection.	Increased, RR 5.01 (3.45–7.28)	Does not reduce ICU mortality or morbidity.
Murad et al. 2012 [46]	Non-ICU outcomes, including AMI and stroke	19 (included non-randomized)	No difference in risk of death, AMI, stroke.	Decreased risk of infection, mainly from surgical studies.	Trend for increased risk	May reduce infection in non-critical care settings.
Bellolio et al., 2011 [49]	Postischemic stroke death and dependency	7	No difference in death or dependency, RR 1.00 (0.78–1.28)	Diabetes: no difference	Increased, RR 25.9 (9.2–72.7)	No difference in death or dependency.
Kramer et al., 2012 [48]	Mortality or neurological outcome after an acute neurological event	16	No difference, RR 0.99 (0.83–1.17)	Less unfavorable neurological outcomes RR 0.91 (0.84–1.00)	Increased, RR 3.10 (1.54–6.23)	Loose control was associated with worse neurological recovery Intermediate control should be target
Ooi et al., 2012 [47]	Outcome in neurological and neurosurgical patients	9	No difference	Reduced infection, better neurological outcomes.	Increased, RR 8.04 (4.85–13.31).	Reduces infection and improves neurological outcome.

guidelines, and is currently limited by cost, the need for staff training, and technical considerations, this may well be an important ICU technology of the future, when attempting tight glucose control. It is routine to continuously or frequently electronically monitor other vital signs so why not glucose as well?

The timing of repeat testing after hypoglycemia is important. The Leuven protocol recommended repeat glucose testing after 1 hour, and the NICE-SUGAR protocol did not call for repeat testing of until 30 minutes after its treatment though it did require that a doctor be called [35•]. It is recommended that conscious patients with even mild hypoglycemia check their blood glucose 15 minutes after treatment [57], and in most hospital wards this would be standard procedure. Delaying repeat testing for 30–60 minutes may result in unnecessarily prolonged exposure to hypoglycemia.

Accuracy of Glucose Testing

Accurate and rapid glucose measurement is essential when targeting tight control in the ICU. In the ICU RCTs, glucose testing has generally been performed with glucometers or arterial blood gas analyzers. However, glucometers were designed for home monitoring where the international industry standard only requires that 95 % of glucose results fall within 0.83 mmol/L at glucose concentrations <4.2 mmol/L and within 20 % at higher concentrations. While some meters outperform this minimum standard, even with an error of 10 %, computer simulations have suggested that 16 %–45 % of insulin doses would be in error when following an insulin dosing algorithm [58]. If testing capillary samples, drug interactions, anemia, and poor tissue perfusion add to the error.

Notably the NICE-SUGAR Study allowed the use of glucometers, and also discouraged, but permitted capillary testing. A systematic review of 11 studies confirmed that glucose measurement using arterial blood was more accurate than capillary blood, relative to laboratory testing, and there was a trend for blood gas analyzers to be more accurate than glucometers in the measurement of arterial blood [59•]. Both methods of measurement were less accurate in the hypoglycemic range, with 11 %–22 % of readings overestimating the glucose level. In ICU blood gas analyzers are usually available so their use should be considered mandatory when aiming for tight glucose control. Whenever possible, arterial lines should be the source of blood for glucose testing.

Other Considerations

Glucose Variability

Experimental studies have found that fluctuating or intermittently elevated glucose levels increases oxidative stress and cell apoptosis [60–62]. Following this, a number of clinical studies have identified an association between glucose variability and increased mortality in coronary care [63, 64] and the ICU [65, 66], and there have been calls to specifically target this [67]. However, an effect of glucose variability on mortality was not seen in the DIGAMI-2 cohort [68], and in a post-hoc analysis of the Leuven studies, intensive insulin therapy did not reduce the standard deviation of the daily glucose readings nor glucose pattern irregularity, suggesting that the lowering of mortality was not related to reduced glucose variability [69]. It remains to be seen how best to address glycemic variability and whether this is truly beneficial beyond the avoidance of hypo and hyperglycemia.

Diabetes vs Stress Hyperglycemia

It has been suggested that the glucose targets for people with diabetes should be less stringent than for people with stress hyperglycemia [70], as the glucose threshold for increased mortality risk is higher for people with diabetes, and the relationship is weaker [12, 71–74]. It is possible that chronic hyperglycemia leads to protective mechanisms in people with diabetes [75], but another explanation may simply be that hyperglycemic people with diabetes are just less unwell, ie, the stress contribution to hyperglycemia is smaller [76].

In the Leuven studies people with diabetes benefited equally from intensive glucose control, and the RABBIT-2 Surgery was conducted in people with diabetes so there is no trial evidence that glucose in people with diabetes should be managed less intensively. Intriguingly,1 observational study found that nonsurvivors had lower glucose levels than survivors if the HbA1c was >6.8 %, so HbA1c may be a better discriminator of patients exposed to chronic hyperglycemia [77], and this should be examined in future RCTs.

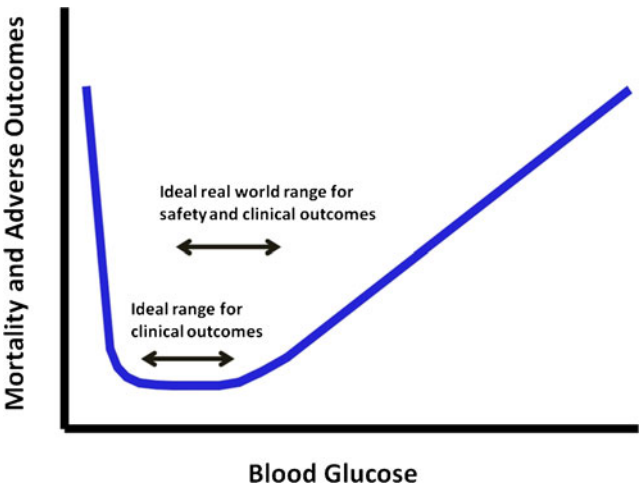

Fig. 1 Relationship between glucose and mortality and adverse outcomes, and the setting of glucose targets

Medical vs Surgical Patients

Several of the meta-analyses suggest that surgical patients benefit more from tight glycemic control, though this is largely driven by the Leuven Surgical ICU study. They also suggest that infection is the complication that is most responsive to tight glycemic control. As surgical patients are at greater risk they may thus derive the greatest benefit. It has been speculated that for medical patients who may have had stress hyperglycemia for some time, adaptive changes to hyperglycemia could have occurred, or the window of opportunity to prevent harm may have passed [52]. Conversely for surgical patients, the onset of hyperglycemia would have been more acute, and therefore prompt glucose control confers more benefit.

There is evidence of benefit of tight glucose control in nonsurgical critical illness [37, 43•], and medical patients are not immune from many of the complications of surgical patients. Therefore it may be premature to set differential glucose targets for surgical and medical patients.

The Evidence for Tight Glucose Control has not Vanished

Some have stated that with the results of NICE-SUGAR the evidence for tight glycemic control in intensive care units has vanished, that stress hyperglycemia is a natural protective phenomenon [78], and recommended that intensive insulin therapy should not be used to strictly control blood glucose in either ICU or non-ICU settings [79]. The alternative view is that glucose control is important, but there are practical factors that need to be considered for tight glycemic control to be safely implemented [52, 80]. There are sufficient concerns about various aspects of the negative trials that one cannot consider them definitive for disproving the benefits of tight glycemic control. Since the publication of the NICE-SUGAR Study, the major piece of original data that has emerged is the RABBIT2-Surgery Study, which indicates that glucose control achieves clinical benefits. Although this was not conducted in critically ill patients, the pathophysiological processes induced by hyperglycemia should be the same regardless of hospital setting.

Perhaps the J Curve association between blood glucose and mortality should be seen as a U-shaped curve that is skewed to the left (Fig. 1). At the hypoglycemic end of the spectrum, there is a sharp rise in risk, but on the hyperglycemia end, the increase in risk is more gradual. Therefore in a situation of critical illness, where there are multiple factors which may impact on glucose measurement and control, it makes sense to aim for a real world target, which accepts a modest increase in risk in the hyperglycemia range, but ensures there is sufficient buffer to avoid hypoglycemia.

The glucose targets currently recommended by most professional bodies have adopted this approach, with most suggesting an upper glucose target of 10 mmol/L (180 mg/dL) across the spectrum of critical illness [81–85], though the Society of Critical Care Medicine recommends a target <8.3 mmol/L [86]. All recommend avoidance of hypoglycemia, with adjustment of glucose lowering therapy at a BG below 3.9–7.8 mmol/L [81, 83, 84, 86]. Ultimately the lower end of the glucose target should be based on what can safely be achieved, and this may depend on local circumstances.

Conclusions

In 2013, sufficient evidence remains to support the practice of tight glucose control in critical illness and it is not going away. Current guidelines are largely pragmatic, developed with safety in mind. Questions remain as to what the ideal glucose target is, and there are practical considerations as to how this can be safely attained.

Compliance with Ethics Guidelines

Conflict of Interest A.E. Wagstaff declares that she has no conflict of interest. N.W. Cheung declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent This article contains studies with human subjects performed by Dr. NW Cheung, who was a chief investigator in the HI-5 and QASC studies, both of which are human studies referred to in this paper. Both studies were approved by Ethics committees and informed consent was obtained from all participants in these studies.

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