Bellomo *Journal of Intensive Care* (2018) 6:71
https://doi.org/10.1186/s40560-018-0336-2

Journal of Intensive Care

COMMENTARY Open Access

Acute glycemic control in diabetics. How sweet is oprimal? Pro: Sweeter is better in diabetes

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Abstract

Background: The optimal level of glycemic control in ICU patients has been the subject of intense investigation over the last 20 years. A pivotal study (the NICE-SUGAR study) involving more than 6,000 patients has established a target between 8 and 10 mmol/l (144 to 180 mg/dl) as the current standard of care. However, this study did not address whether patients with diabetes should be treated differently and, in particular, whether in such patients a higher glucose target should be used.

Main concepts: The last decade has seen multiple studies aiming to describe the association between glycemia in mortality according to whether patients have or do not have diabetes and whether, if they have diabetes, pre-ICU admission glucose control (assessed by glycated hemoglobin A1c (HbA1c) levels) affects the relationship between acute glycemia and outcome. All such studies (now involving thousands and thousands of patients) have consistently shown that diabetic patients have a different relationship between acute glycemia and mortality. In particular, in diabetic patients, increasing glucose levels up to 15 mmol/l (270 mg/dl) or more are not associated with increased risk of death. In patients with a high HbA1c (> 7%) prior to ICU admission, targeting a glucose level below 10 mmol/l (180 mg/dl) is associated with increased risk compared with permissive hyperglycemia. Finally, a recent controlled study comparing a glucose target between 10 and 14 mmol/l (180 to 252 mg/dl) to a glucose target between 6 and 10 mmol/l (180 mg/dl) in diabetic patients found no advantage from tighter glycemia control. A randomized controlled study called LUCID is now underway to test the hypothesis that permissive hyperglycemia might be safer in diabetic patients admitted to the ICU.

Conclusions: Until the results of the LUCID trial are available, the burden of evidence is in favour with targeting a more relaxed level of glycemia in diabetic patients (10–14 mmol/l; 180–252 mg/dl), especially in those with poor pre-admission glycemic control.

Keywords: Glucose, Glycemia, Diabetes, Insulin, Randomized controlled trial, Hyperglycemia, Hypoglycemia

Background

Current guidelines recommend insulin therapy to maintain a blood glucose level (BGL) below 10 mmol/l in all critically ill [1–3] and cardiac surgery patients [4]. These guidelines are supported by the findings of a pivotal trial: the Normoglycemia in Intensive Care Evaluation Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial. The NICE-SUGAR trial found that, in ICU patients, targeting a glucose of 8–10 mmol/l (144–180 mg/dl) compared with target glucose of 4.5–6.0 mmol/l (81–108 mg/dl) [5] reduced all-cause mortality at 90 days. However, in NICE-SUGAR, only limited information was available regarding premorbid glycemic control, diabetic status, and outcome. In particular, there was no information as to whether patients with diabetes would have a better outcome if their mean glycemia in the ICU was allowed to exceed 10 mmol/l (180 mg/dl). This issue is highly relevant to the approximately 25% of patients with diabetes who are currently admitted to ICUs in Western countries and who

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appear to be significantly different in terms of their relationship between acute glycemia and outcome.

Main concepts

Patients with diabetes appear to respond differently to "conventional" glucose control compared with non-diabetic patients. For example, among type 2 diabetes patients with a glycated hemoglobin A1c (HbA1c) ≥ 7% (implying an average BGL of ≥ 8.5 mmol/l [153 mg/dl]; [6]), an average glucose level between 10 and 14 mmol/l (180–252 mg/dl) in the intensive care unit (ICU) was associated with lower mortality compared with recommended target levels [7]. Moreover, a large observational study found an association between diabetes and increased risk of hypoglycemia and mortality when conventional glucose control was applied in the ICU [8]. These observations suggest that a more liberal glycemic level (between 10 and 14 mmol/l) (180–252 mg/dl) in ICU patients with diabetes may both be safe and perhaps desirable [9–12]. Preliminary data support the notion that such "liberal" glycemic management may be particularly safe and desirable in those diabetic patients who have suboptimal pre-admission chronic glycemic control as shown by their HbA1c levels [10, 12]. However, until recently, there were limited controlled data to support these implications of observational studies. More recently, however, a controlled trial comparing conventional with liberal glycemic control in diabetic ICU patients was completed: the *S*afety of Gl*U*cose *E*levation *E*valuation *T*rial (SUEET) (ACTRN12615000216516) [13].

SUEET was a prospective, open-label, sequential, before-and-after study in ICU patients with diabetes. It aimed to compare the impact of liberal (10–14 mmol/l) (180–252 mg/dl) versus conventional (6 to 10 mmol/l) (198–180 mg/dl) glycemic control. SUEET compared 350 consecutive patients with diabetes who received liberal glucose control with a pre-intervention control population also of 350 consecutive patients with diabetes who received conventional glucose control.

SUEET found that liberal glycemic management decreased insulin therapy requirements and lowered glucose variability. It also found a trend towards decreased incidence of hypoglycemia with liberal glycemic control among those patients with HbA1c ≥ 7%. In addition, it found no difference in mortality (even after adjustment of baseline characteristics), duration of mechanical ventilation, or ICU-free days to day 30. Finally, it found no evidence of harm from liberal glycemic management in any patient subgroup.

SUEET also provided further insights into the consequences of liberal glycemic control in diabetic patients. For example, it found that almost half of glucose values spontaneously remained below 10 mmol/l (180 mg/dl) and that only a third of patients required insulin to maintain glucose levels within the target range. This observation implies that a liberal approach to glycemic control leads to no insulin-based intervention in 50% of diabetic ICU patients.

Furthermore, in keeping with the results of a pilot study of patients with a HbA1c ≥ 7%, where implementation of liberal glucose control was associated with half the risk of hypoglycemia, subgroup analysis of > 300 patients with a HbA1c ≥ 7% confirmed such benefits with a decrease in the incidence of hypoglycemia from 9.6 to 4.1%. Similarly, SUUET found that liberal control did not contribute to worsening kidney function in patients with diabetes. Moreover, the lack of a difference in the trajectory of white cell count during the first week in the ICU despite significant differences in glycemia suggests that concerns about increased risk of infection are unlikely to be correct.

Patients with diabetes reliably show no independent association between mean [14, 15] or peak glucose [16] and mortality. Among patients with HbA1c ≥ 7%, those with average blood glucose of 10–14 mmol/l (180–252 mg/dl) in the ICU appear more likely to survive to hospital discharge than those with a concentration in the conventional range [8]. Moreover, in patients with marked chronic hyperglycemia (HbA1c > 8.5%), acute hyperglycemia, and glycemic variability are not associated with increased mortality [16, 17]. Similarly, in a recent sequential period analysis of > 400 ICU patients with diabetes, Krinsley et al. assessed the impact of HbA1c-guided glycemic control on outcomes. These investigators delivered a "tighter" target in patients with HbA1c < 7% and a "looser" target in those with HbA1c ≥ 7%. Compared with their control period, such HbA1c-adjusted glycemic control significantly reduced the observed-to-expected mortality ratio [12]. Moreover, a large observational study of thousands of patients with diabetic ketoacidosis recently found that permissive hyperglycemia was associated with significantly greater survival compared with achieving a glucose level < 10 mmol/l in the first 24 h of ICU admission [18]. In their aggregate, these studies suggest that "permissive hyperglycemia" in ICU patients with diabetes, who are likely adapted to some degree of chronic hyperglycemia, is safe. Nonetheless, this field is evolving rapidly, with new interventions being considered [19], new technology being applied to glucose monitoring in the ICU [20], and the need to focus on long-term outcomes [21] all becoming new focuses of investigation.

Conclusions

In summary, the above observations consistently suggest that liberal glucose control to a target between 10 and 14 mmol/l (180–252 mg/dl) decreases insulin administration requirements, lowers glucose variability, and reduces the risk of hypoglycemia, especially among those patients with poor pre-morbid glycemic control. Moreover, they suggest that insulin administration to maintain blood glucose within the conventional target range may be

unnecessary in many critically ill patients with diabetes, irrespective of their premorbid glycemic control, illness severity, reason for ICU admission, and septic state. Finally, they justify the performance of a multicentre randomized controlled trial of liberal glycemic control in patients with diabetes. Such a trial (www.anzctr.org.au; ACTRN12616001135404) is now underway. Until the results of such trial (the *L*iberal Gl*U*cose **C**ontrol in Critically *I*ll Patients with Pre-existing Type 2 *D*iabetes trial—the LUCID trial) are available, the weight of evidence is clearly in favour of the concept that, in diabetic patients admitted to the ICU, sweeter is better.

Abbreviation
Hba1c: Glycated hemoglobin A1c

Author's contributions
This commentary was written solely by RB (the author). The author read and approved the final manuscript.

Ethics approval and consent to participate
Not applicable

Consent for publication
Not applicable

Competing interests
The author declares that he has no competing interests.

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Received: 5 September 2018 Accepted: 27 September 2018
Published online: 08 November 2018

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Egi *Journal of Intensive Care* (2018) 6:70
https://doi.org/10.1186/s40560-018-0337-1

Journal of Intensive Care

REVIEW Open Access

Acute glycemic control in diabetics. How sweet is oprimal? Con: Just as sweet as in nondiabetic is better

Moritoki Egi

Abstract

This review is for Con side of "Pro-Con debate" on the optimal target of blood glucose levels in patients with chronic hyperglycemia (e.g. premorbid HbA1c level > 7%). Currently, international guideline recommended that blood glucose level ≤ 180 mg/dL in critically ill patients irrespective of presence or absence of premorbid diabetes. However, there are several studies to generate the hypothesis that liberal glycemic control (e.g., target blood glucose level 180–250 mg/dL) may be beneficial in critically ill patients with premorbid hyperglycemia. Although there is before-after study to report its safety and feasibility, it should be noted that this strategy may have a potential to increase the risk of infection, glycosuria, and polyneuropathy. Furthermore, there is randomized controlled study which showed the potential harm of liberal glycemic control in patients with premorbid hyperglycemia. Additionally, there are lots of uncertainty about the candidate and methodology of such a permissive hyperglycemia. With considering these facts, it might be better to keep target of blood glucose level in patients with diabetes the same as patients without diabetes (≤ 180 mg/dL), until randomized control study as like LUCID (the Liberal GlUcose Control in Critically Ill Patients with Pre-existing Type 2 Diabetes) trial will justify its risk and benefit.

Keywords: Diabetes, Chronic, Hyperglycemia, Liberal

Background

This review is one of "Pro-Con" reviews to discuss the optimal target of blood glucose levels in patients with chronic hyperglycemia (e.g., premorbid HbA1c level > 7%). It is for the "Con" side standing for the statement that optimal target of acute glycemic control in patients with chronic hyperglycemia was same as in non-diabetic patients (≤ 180 mg/dL).

Although intensive insulin therapy (target blood glucose 80–110 mg/dL) had been reported to lower the mortality in a single-center randomized controlled trial [1], cumulative evidences show that such a glycemic management had significantly higher incidence of hypoglycemia and no further merit on the mortality and morbidity. According to the results of NICE-SUGAR trial [2] and subsequent meta-analysis [3], international guideline for management of sepsis recommended to maintain blood glucose level ≤ 180 mg/dL in acute illness [4, 5].

How differently the target of blood glucose level is recommended in patients with and without diabetes

NICE-SUGAR trial had reported that intensive glucose control increased mortality among adults in the ICU. In other words, a blood glucose target of ≤ 180 mg/dL resulted in lower mortality than did a target of 81 to 108 mg/dL [2]. This effect was not significantly different between patients with and without diabetes ($p = 0.60$). Recently, one study reported estimation of optimal blood glucose level in critically ill patients using network meta-analysis [6]. However, this study could not analyze the optimal target in acute ill patients with premorbid diabetes due to the limit of evidence. Accordingly, current guideline recommends the same target of blood glucose level (≤ 180 mg/dL) irrespective of presence or absence of premorbid diabetes [5].

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The liberal glycemic control in critically ill patients with chronic hyperglycemia

There are studies shown that relationship between hyperglycemia and outcomes was altered by the presence of diabetes mellitus [7–12]. Furthermore, there are studies reported that premorbid hyperglycemia might interact the relationship between acute glycemic control and mortality [13–15]. Accordingly, these observational studies suggest that a liberal glycemic level (e.g., between 180 and 250 mg/dL) in critically ill patients with chronic hyperglycemia may be beneficial [16–19].

However, there are limited controlled studies to justify the benefit or harm of such a liberal glycemic control in particular cohort. Recent before-after study conducted in critically ill patients with diabetes shows that liberal glucose control was associated with decrease in insulin administration without any difference on clinical outcomes. This study also showed that the incidence of hypoglycemia was decreased in patients with chronic hyperglycemia [20]. However, there are several concerns on such a "permissive hyperglycemia" in critically ill patients with diabetes.

There are concerns of liberal glycemic control in patients with diabetes

First concern on the "permissive hyperglycemia" in patients with diabetes is the risk of infection. Rayfield et al. had reported that there is significant association of mean glycemia and the risk of infection in diabetic patients [21]. There is a diminution in intracellular bactericidal activity of leukocytes and lower serum opsonic activity for bacteria in patients with poorly controlled diabetes. It should be noted that Centers for Disease Control and Prevention Guideline for the prevention of surgical site infection recommends to avoid the hyperglycemia as 200 mg/dL in patients with and without diabetes (category IA—strong recommendation; high to moderate—quality evidence) [22].

Second concern is the risk of glycosuria. Ruhnau et al. conducted prospective study to assess the renal threshold for glucose in patients with non-insulin-dependent diabetes [23]. At the level of 180 mg/dL of blood glucose, about half of the patients had partial glycosuria and the rest had no glycosuria. However, at the level of 250 mg/dL, approximately two thirds of the patients had persistent glycosuria. In critically ill patients, to maintain intravenous blood volume is relevant. Therefore, we might be able to prevent the glycosuria accompanied with permissive hyperglycemia.

Third concern is the risk of polyneuropathy. The polyneuropathy is common in patients with longer duration of diabetes and chronic hyperglycemia [24]. The analysis of pooled dataset of two randomized controlled trials shows that lowering blood glucose control had a non-significant trend to decrease the incidence of critical illness-induced polyneuropathy in patients with diabetes (43.9% vs 32.6%; odds ratio = 0.62, $p = 0.25$) [25]. These findings may suggest that hyperglycemia might be better to be avoided to prevent polyneuropathy in critically ill patients with diabetes.

In different words, these three concerns might suggest that conventional control may be beneficial to lower the risk of infection, to avoid the derangement due to the glycosuria, and to prevent the polyneuropathy in comparison with the liberal glycemic control in acute ill patients with chronic hyperglycemia.

The randomized controlled trial to assess "permissive hyperglycemia" in acute ill patients with hyperglycemia

The DIGAMI study is a multicenter randomized controlled trial comparing between blood glucose level < 198 mg/dL and no use of insulin in post-myocardial infarction patients with HbA1c of around 8% [26]. The blood glucose level 24 h after randomization in no insulin group was 211 mg/dL in average, which is significantly higher than those of 173 mg/dL in the group of < 198 mg/dL. In the DIGAMI study, blood glucose control < 198 mg/dL significantly reduced 1-year mortality in comparison with those without using insulin. As DIGAMI study was conducted 25 years ago, their finding may not be generalized into current practice. Nonetheless, we should note that there is interventional study to show that the permissive hyperglycemia may increase the mortality in comparison with current usual glycemic control in patients with premorbid hyperglycemia.

Conclusion

Liberal glycemic control is the concept of permissive acute hyperglycemia in critically ill patients with premorbid hyperglycemia. Although there are several studies to support this hypothesis and to report its safety and feasibility, we should note that this strategy may have a potential to increase the risk of infection, glycosuria, and polyneuropathy. Furthermore, there is randomized controlled study which showed the potential harm of liberal glycemic control in patients with premorbid hyperglycemia. Additionally, there are lots of uncertainty about the candidate and methodology of such a permissive hyperglycemia.

Considering above facts, it might be better to keep target of blood glucose level in patients with diabetes as same as in patients without diabetes (≤ 180 mg/dL), until randomized control study as like LUCID (the Liberal GlUcose Control in Critically Ill Patients with Pre-existing Type 2 Diabetes) trial justify its risk and benefit.

Funding
This work was supported by Grant-in-Aid for Scientific Research (16K10936).

Authors' contributions
ME conceptualized, drafted, critically revised, and approved the final manuscript.

Ethics approval and consent to participate
Nil as this is review article

Consent for publication
Nil as this is review article

Competing interests
The authors declare that they have no competing interests.

Publisher's Note

Received: 2 September 2018 Accepted: 27 September 2018
Published online: 06 November 2018

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