Editorial

Acute severe illness in diabetes patients: is tolerating hyperglycemia beneficial?

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Due to the severe stress evoked by major surgery, a major trauma or a severe medical illness, critically ill patients commonly develop hyperglycemia. Repeatedly, in divergent patient populations and in both critically ill adults and children, observational studies have shown a U-shaped association between glycemic levels in the intensive care unit (ICU) and the risk of death, with the lowest risk of death associated with glucose levels that are normal for age (1,2). Of course, association does not imply causation, which can only be determined by a randomized controlled trial (RCT) interfering with hyperglycemia. Three proof-of-concept RCTs in Leuven demonstrated that both morbidity and mortality were reduced by treating severe hyperglycemia [>215 mg/dL (11.9 mmol/L)] with insulin to target normal for age glucose levels [80–110 mg/dL (4.4–6.1 mmol/L) for adults, 60–100 mg/dL (3.9–5.6 mmol/L) for children, 50–80 mg/dL (2.8–4.4 mmol/L) for infants], which strongly suggested a pathophysiological role of hyperglycemia in critical illness (3-5). Subsequent mechanistic studies pointed to a crucial role of preventing glucose overload to vital organs as mediator of organ protection by tight glycemic control (TGC) (6). Following the pioneer studies in Leuven, multiple centers worldwide adopted this seemingly simple intervention and several implementation studies and single center RCTs confirmed a protective effect by targeting normoglycemia by insulin therapy (7-9). Implementation of some degree of glycemic control in ICUs worldwide impeded a repeat multicenter RCT that used the same glycemic targets as in the Leuven studies. Indeed, multicenter trials no longer randomized patients to TGC versus a liberal glycemic target, but used an intermediate glycemic target in the control group, in general <180 mg/dL (10 mmol/L). In contrast to the landmark studies, these multicenter trials found that compared to an intermediate glycemic target, targeting TGC no longer provided benefit and could even be harmful as found in NICE-SUGAR (10-13). Therefore, most current guidelines recommend to target glycemia <180 mg/dL (10 mmol/L) in critically ill patients (14,15). However, no adequately powered RCT has directly compared the recommended intermediate glycemic target versus a liberal target. Moreover, besides a different glycemic target in the control group, several other methodological differences may account for the divergent results between the Leuven studies and subsequent multicenter trials, in particular the NICE-SUGAR study. These differences include, among others, the use of inaccurate glucose measurement tools and unvalidated glucose control algorithms as well as different feeding regimens (16). Hence, the optimal glycemic target in critically ill patients remains unclear.

Another factor that may alter the effect of TGC in critical illness is the presence of pre-admission diabetes mellitus. In a recent issue of *Diabetes Care*, Greco and colleagues investigated the relationship between postoperative glucose levels and outcome after cardiac surgery (17). In patients without pre-existing diabetes mellitus and in patients with diabetes not treated with insulin, corrected for baseline risk factors, they found significantly worse outcomes when peak glycemia in the first 48 hours was above 180 mg/dL (10 mmol/L). In contrast, in patients with insulin-treated diabetes mellitus, this relationship was not significant in adjusted analysis and there was a non-significant trend towards a better outcome in patients with at least one measurement >180 mg/dL (10 mmol/L).

Based on their results, the authors call for further investigation of an approach that adapts the glycemic control regimen based on the diabetes status.

The study was performed on a large dataset, which is one its strengths. In addition, for several analyses they adjusted for a large number of risk factors. However, the study clearly has its limitations. Due to the observational nature, the authors cannot establish a causal link, which the authors clearly acknowledged. In addition, by studying outcome in relation to the peak glycemia in the first 48 hours postoperatively, they did not take into account the mean glycemia over the whole ICU stay, which would be a more relevant value from a physiological point of view. In addition, if hyperglycemia would be advantageous in insulin-treated diabetics, one would expect that patients with at least two hyperglycemic measurements would perform better than patients with only one measurement in that range, which was apparently not the case. It is also unclear why the authors did not always correct for all baseline risk factors (17).

To put the current study in a wider perspective, it is important to resume other studies in the field. Whereas several observational studies have indicated a flattening of the U-shaped relationship between glycemia in ICU and outcome in diabetes patients compared to non-diabetes patients, the lowest mortality risk in most studies associated with normal or slightly elevated glucose levels and not with severely hyperglycemic values (1,7,18). Moreover, several large implementation studies have observed that implementation of a TGC protocol also improved mortality in diabetes patients (7,19).

To study the relationship of glycemia with outcome, Greco *et al.* further divided diabetics regarding the diabetes treatment they received (17). Whereas non-insulin-treated diabetics behaved similarly as non-diabetics, with worse outcomes when peak glycemia exceeded 180 mg/dL (10 mmol/L), insulin-treated diabetics apparently had a better outcome when peak glycemia exceeded that value. The physiological background for this apparent difference is unclear. Other observational studies have suggested that the optimal glycemic target in diabetics may depend on the pre-existing level of glycemic control, as reflected by the pre-admission HbA1c (20,21). From a physiological point of view, this appears more plausible, as patients may adapt to chronic hyperglycemia (22). In addition, an observational study has suggested that especially patients with prolonged hyperglycemia before ICU admission (HbA1c ≥8%) are more prone to severe hypoglycemia [<40 mg/dL (2.2 mmol/L)] (23). In addition, these investigators found that only in this patient group severe hypoglycemia independently associated with mortality (23). Apart from the different diabetes treatment, the opposite relationship between glycemia and outcome in the current study of Greco could be explained by a difference in pre-admission glucose levels. Indeed, the HbA1c was significantly different between insulin-treated and non-insulin-treated diabetics, with a significantly higher HbA1c (or higher mean glucose levels) in insulin-treated diabetics (17).

As mentioned above, to establish a differential impact of hyperglycemia in diabetics compared to non-diabetics with critical illness, an RCT is needed. Preferentially, rather than diabetes treatment (insulin or not), this RCT should take the premorbid level of glycemic control into account. Currently, however, no RCT has shown opposite effects in critically ill diabetics versus non-diabetics. Indeed, subgroup analyses of existing RCTs either have found no difference in outcome or an attenuated effect in critically ill diabetics versus non-diabetics (10,13,24).

In conclusion, fifteen years of research on TGC in critically ill patients have learned that it is a complex intervention. Safe and effective implementation requires accurate monitoring of glycemia and an effective protocol, which can be achieved with the use of a validated glucose control algorithm. The influence of the feeding regimen remains to be investigated. Currently, the optimal target glycemia for critically ill diabetes patients is unclear, as is the case for non-diabetes patients. Whether the glycemic target should be individualized and be based on the pre-existing degree of glycemic control is the scope of a currently recruiting RCT (25). Until new evidence from RCTs is available, common sense supports to prevent severe hyperglycemia in all ICU patients.

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Footnote

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