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What's new in glucose control in the ICU?

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It is 12 years now since the first randomized controlled trial (RCT) showed that targeting strict normoglycemia (80–110 mg/dl in adults) in ICU patients prevented excess morbidity and mortality as compared with tolerating stress hyperglycemia up to 215 mg/dl [1]. Yet, the topic remains as "hot" as ever, reflected by the more than 500 papers published in 2012.

Clearly, the interest in the pathophysiology of metabolic disturbances during illness has not waned and the controversy on how to optimally treat hyperglycemia in the ICU is continuing. Nevertheless, updated practice guidelines, such as those by the Surviving Sepsis Campaign, firmly advise to treat hyperglycemia in ICU patients to levels below 180 mg/dl [2]. These recommendations acknowledge that it remains unclear whether further lowering of blood glucose to "normal" levels can safely evoke benefit or instead may induce harm, given the high incidence of hypoglycemia uniformly associated with such tighter blood glucose control. The recommendations appear to be well implemented in daily practice, as shown by a recent study reporting that most ICUs have an insulin protocol in place for the almost 90 % of patients achieving blood glucose levels well below the currently recommended 180 mg/dl [3]. Whereas in the early years after the 2001 Leuven publication [1], many ICUs had adopted strict normalization of blood glucose, this strategy is now often abandoned in favor of a more loose approach. This is mainly triggered by the results of the NICE-SUGAR trial, which in the multicenter setting of Australia, New Zealand, and Canada showed that such intermediate, looser blood glucose target evoked less hypoglycemia and lower risk of death than the strict normoglycemia target [4] (Fig. 1). Whether "loosening" blood glucose control in clinical practice, in response to NICE-SUGAR, is a wise decision remains debated. Indeed, a recent study documented the impact of this loosening in centers that were using a computerized algorithm to titrate insulin to target blood glucose values, and found that this loosening increased mortality in

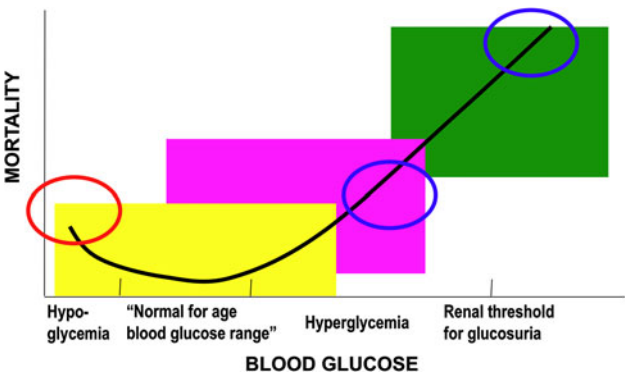

Fig. 1 Cartoon depicting risk of death in relation to blood glucose levels during critical illness. *Yellow* and *pink areas* reflect blood glucose ranges achieved with tight blood glucose control in studies with an intermediate blood glucose target in the control group and using inaccurate blood glucose sensors; *green area* reflects blood glucose levels achieved when no insulin is advised except when exceeding the renal threshold. *Red circle* reflects the risk of hypoglycemia, a risk that is traded off against the risk of hyperglycemia, which is moderate or high depending on the control group reflected by the *blue circles*. The trade-off between these risks may determine the net outcome of studies on blood glucose control

non-diabetic ICU patients, as compared with the previously applied tighter glucose control [5]. Within the same institute, it is clearly easier to document the impact of just slightly altering the target for blood glucose, as all other confounders, related to the complex procedure of titrating insulin to a certain blood glucose value, are kept constant.

Also in 2012, one was reminded that these confounders comprise the type and accuracy of the instrument used to measure blood glucose concentrations [6], the level of experience of nurses [7], and also the way of infusing insulin [8]. The last of these pitfalls, previously identified in the 2001 Leuven study, was not well appreciated in subsequent repeat studies. The recent study by Maury et al. [8] showed that when insulin is infused via a central venous catheter lumen also used for on-demand medication injections, this leads to flushes of insulin whereby iatrogenic hypoglycemia and glucose fluctuations, both of which go unnoticed in the routine clinical practice of only intermittently measuring blood glucose. So not only should glucose sensors be accurate and standardized and nurses be trained or advised by effective computer algorithms based on proof-of-concept studies [9], but also confounding factors such as accidental insulin flushes should be carefully avoided before the benefit of more subtle differences in target levels for blood glucose can be investigated in intervention studies. Standardization is key and also applies to such details.

The main risk of implementing insulin therapy to target any level of blood glucose concentration is hypoglycemia. Hypoglycemia is considered to be harmful and thus the price to pay for our attempts to reduce or prevent hyperglycemia in the ICU. However, whether brief hypoglycemia in the ICU setting is a marker or a mediator of "harm" is still debated. In 2012, several research publications showed that this question of causality is not a simple one to answer. The post hoc observational analysis of the NICE-SUGAR trial identified hypoglycemia with insulin treatment as an independent risk factor, thereby likely explaining the increased mortality [10]. Of course it is impossible to specifically investigate the impact of hypoglycemia by an RCT design, which makes it hard to robustly conclude on the causality of such associations. One study that was published in 2012, and that comes as close as possible to such an RCT, is the study by Mesotten et al. [11], which documented the long-term neurocognitive developmental impact of targeting age-normal fasting blood glucose (50–80 mg/dl in infants and 70–100 mg/dl in children) in critically ill children versus tolerating stress hyperglycemia up to 215 mg/dl. In this RCT, targeting such low levels of blood glucose evoked brief, though severe, hypoglycemia in 1 out of 4 children, a number that rose to 1 in 2 when considering infants only. If such brief hypoglycemia is causing any harm to the vulnerable, developing brain, the high incidence in this trial should have allowed one to detect it in the long-term follow-up. Strikingly, the intervention did not cause the slightest harm and actually improved certain areas of cognition. These findings are in line with what was subsequently reported in a study of premature newborns, where hypoglycemia also did not cause any harm to brain development [12]. This is important novel evidence, as when higher blood glucose levels were targeted in ICU children, aiming to avoid hypoglycemia, blood glucose was not significantly lowered and, not surprisingly, outcome was unaffected [13]. In line with these observations, a recent meta-analysis of studies in neurosurgical ICU patients showed that tight glucose control improved neurological outcome [14]. And in a study investigating human brain specimen from patients who took part in two RCTs on tight glucose control, and in brains harvested from an animal model, Sonneville et al. [15] showed that hyperglycemia, not hypoglycemia, dose-dependently damages neurons by increasing brain inflammation.

Important novel insights from the last year support the need for more research on the topic of blood glucose control during critical illness. Given the complexity of the intervention, previously not fully appreciated by clinicians and researchers [4, 16], new studies will need better tools to better standardize the treatment. So, after 12 years, the jury is still out.

Conflicts of interest No conflict of interest to report.

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