CRITICAL CARE

VIEWPOINT

Critical illness-induced dysglycaemia: diabetes and beyond

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Abstract

Type 2 diabetes has reached epidemic proportions in many parts of the world. The disease is projected to continue to increase and double within the foreseeable future. Dysglycaemia develops in the form of hyperglycaemia, hypoglycaemia and marked glucose variability in critically ill adults whether they are known to have premorbid diabetes or not. Patients with such glucose dysregulation have increased morbidity and mortality. Whether this is secondary to cause and effect from dysglycaemia or is just related to critical illness remains under intense investigation. Identification of intensive care unit (ICU) patients with unrecognised diabetes remains a challenge. Further, there are few data regarding the development of type 2 diabetes in survivors after hospital discharge. This commentary introduces the concept of critical illness-induced dysglycaemia as an umbrella term that includes the spectrum of abnormal glucose homeostasis in the ICU. We outline the need for further studies in the area of glucose regulation and for follow-up of the natural history of abnormal glucose control during ICU admission and beyond.

Type 2 diabetes is one of the greatest challenges facing healthcare professionals. The general population disease prevalence is approximately 2.8% worldwide [1]. In contrast, the most recent US National Health and Nutrition Examination Survey estimates that 12.9% of US ambulatory adults over 20 years of age have type 2 diabetes [2]. The prevalence of diabetes is expected to double over the next 30 years due to increased age, inactivity and obesity [1].

Complicating this phenomenon is the knowledge that approximately 40% of patients with diabetes remain

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undiagnosed [2]. These patients cannot be treated, and are vulnerable to short-term and long-term complications [3-5]. The true prevalence of diabetes in hospitalised patients is not known, due to the heterogeneous patient population and limitations in diagnostic tests [6]. The prevalence in intensive care unit (ICU) patients is perhaps 25% or higher, depending on unit specialty and patient demographics [6].

Adults with diabetes have at least double the annual mortality compared with adults without diabetes [7]. Paradoxically, several studies of hospitalised patients have demonstrated that hyperglycaemic individuals without known diabetes have significantly greater morbidity and mortality than either patients with known diabetes or those with normal glucose tolerance [8-11]. Hyperglycaemic patients without diabetes include those with undiagnosed diabetes, prediabetes (impaired fasting glucose and impaired glucose tolerance) or stress-induced hyperglycaemia (SIH) – defined as patients with elevated blood glucose that reverts to normal after illness subsides and counterregulatory hormone and inflammatory mediator surge abates [6]. Large, retrospective studies in critically ill adults have shown that hyperglycaemic patients with diabetes have lower ICU and hospital mortality and shorter length of ICU stay than critically ill hyperglycaemic patients without diabetes [8-10]. This increased mortality in hyperglycaemic patients without diabetes occurs despite this population having lower absolute glucose levels than those with diabetes. Similar findings were reported in hospitalised general care patients [11].

How can this paradox be explained? First, patients without diabetes may have unexpected hyperglycaemia that is frequently left untreated. Umpierrez and colleagues showed that insulin therapy was provided to 77% of patients with known diabetes, compared with 35% of hyperglycaemic patients without diabetes [11]. Second, the critically ill nondiabetic hyperglycaemic population comprises patients with undiagnosed diabetes and patients with SIH [6,12]. Whether hyperglycaemia and adverse outcomes in the nondiabetic cohort are due to SIH, or are simply a marker of severity of illness, remains unknown. Prospective studies with clearly defined

Table 1. Factors impacting critical illness-induced dysglycaemia

Continued growth of abnormal glucose homeostasis in adults
Heterogeneous intensive care unit patient population
Uncertainty as to whether hyperglycaemia may cause adverse outcomes, or may simply be the effect of counterregulatory hormone surge indicating severity of illness
Need for further clarification of the incidence of co-existing factors in the development of and role of hypoglycaemia (<80 mg/dl) on intensive care unit outcome
Ongoing debate over the ideal method and frequency of glucose measurement, the optimal glucose level to maintain in adult intensive care unit populations, and the modulation of glucose variability

nondiabetic cohorts are needed to differentiate between undiagnosed diabetes and SIH.

Accurately diagnosing hyperglycaemic ICU patients with new diabetes while they are still hospitalised, however, remains difficult. Fasting plasma glucose values and oral glucose tolerance tests can only be used in ICU survivors after discharge, as these tests are inaccurate during critical illness [6,12]. Recently endorsed by the International Expert Committee [13] and the American Diabetes Association as a diagnostic criterion for diabetes mellitus [14], haemoglobin A_{1c} may prove useful in categorising inpatients [15]. But haemoglobin A_{1c} must be used carefully, as it may be inaccurate in conditions that shorten or prolong the survival of erythrocytes and in patients receiving blood transfusions [13]. Likewise, its value may vary by racial or ethnic group [16]. Ambulatory follow-up at 6 to 8 weeks post recovery affords the best opportunity to look back and diagnose type 2 diabetes [12].

Owing to these limitations, few studies have attempted to define the true prevalence of diabetes in ICU patients with unexpected inpatient hyperglycaemia. Recently, Mullhi and colleagues showed in ICU survivors (n = 30) with new hyperglycaemia that 46.7% (n = 14) had undiagnosed diabetes and 30% had a prediabetes state (n = 9 impaired fasting glycaemia or glucose tolerance) during their ICU stay [17]. Similarly, the natural history of ICU patients with inpatient hyperglycaemia but without diabetes merits further study. Gornik and colleagues recently reported that 15.2% of septic ICU patients with documented SIH and normal, post-discharge glucose tolerance developed diabetes within 5 years of hospital discharge, versus 4.2% of normoglycaemic ICU patients [18]. The authors hypothesised that stress may uncover latent metabolic disturbance. Gornik and colleagues presented very similar findings in *Critical Care* about the development of type 2 diabetes in 17.1% of patients with SIH among nearly 600 heterogeneous critically ill patients followed for 5 years after ICU discharge [19]. These longitudinal data reveal the importance of continued surveillance of this high-risk population.

Inpatients may also experience other types of glucose dysregulation. Large, randomised controlled trials from the past decade, which investigated the impact of preventing pronounced hyperglycaemia during critical illness with insulin infusion, report increased mortality associated with hypoglycaemia [20-23]. Egi and colleagues showed that increased mortality in mildly hypoglycaemic patients (blood glucose <80 mg/dl) may be independent of insulin use [21]. Their findings suggest that altered glucose metabolism, as well as exogenous overtreatment with insulin, may play a meaningful role in critical illness and mortality. In a retrospective cohort analysis of 7,820 patients with acute myocardial infarction, Kosiborod and colleagues reported that patients who developed spontaneous hypoglycaemia had an increased mortality while those who developed it secondary to insulin therapy did not [24]. Several studies have also demonstrated increased mortality with either hypoglycaemia or hyperglycaemia [20,21]. Glucose variability may confer an adverse risk of mortality, independent of absolute glucose level [23] – although recently the Leuven group retrospectively analysed their two large prospective glucose control trials, and determined that the reduced mortality observed with intensive insulin therapy in the trials was not attributable to an effect on blood glucose variability [25]. The accompanying editorial by Krinsley, however, raised additional factors such as frequency of hypoglycaemia and method of glucose measurement that may have influenced these findings [26]. Limitations in existing glucose monitoring technology further complicate the above issues. This difficulty cannot be ignored when applying protocols to control and regulate blood glucose [27].

We suggest a broader view of glucose dysregulation in the critically ill patient based on numerous factors (Table 1). We apply the term critical illness-induced dysglycaemia to patients with hyperglycaemia, hypoglycaemia or glucose variability. Patients without diabetes, but with other features of critical illness-induced dysglycaemia, appear to be at risk to develop overt type 2 diabetes. These patients should undergo longitudinal evaluation and intervention for the development of subsequent type 2 diabetes.

The decade ending in 2009 witnessed an explosion in publications about ICU glycaemic control, beginning

with the landmark Leuven trial in 2001 [28]. Formal recommendations in 2004 endorsed tight glycaemic control [29]. The decade ended with the 2009 publication of the NICE-SUGAR study [22], and less stringent critical care glucose control guidelines [30]. The concept of critical illness-induced dysglycaemia encompasses all of these factors. We issue a call to recognise the heterogeneous inpatient hypoglycaemic or hyperglycaemic population, in order to study hyperglycaemic subpopulations, to determine diagnostic alternatives for diagnosis of unrecognised inpatients with diabetes, and to develop better monitoring and application of safe, closed-loop systems.

Abbreviations
ICU, intensive care unit; SIH, stress-induced hyperglycaemia.

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

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