# Critically Ill Diabetic Patients

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**The Case for Liberal Glycaemic Management**

**Background**

Several large randomised controlled trials (RCTs) have helped provide evidence to guide clinicians' decisions about blood glucose management in critically ill patients. In two landmark single centre studies, investigators from Leuven reported a reduction in mortality or morbidity with tight glycaemic control (80-110 mg/dl or 4.4-6.1 mmol/L) in critically ill patients (Van den Berghe et al. 2001; 2006). However, the findings of five more recent intensive care-based RCTs, including the very large (>6,000 patients) NICE-SUGAR trial, were unable to replicate these findings (Finfer et al. 2009; Brunkhorst et al 2008; De La Rosa et al 2008; Arabi et al 2008), and in the case of NICE-SUGAR they actually found harm with tight glycaemic control. The aggregate findings of such trials have therefore led to recommendations to target blood glucose levels below 180 mg/dl (10 mmol/L) in order to avoid excessive hyperglycaemia and minimise the risk of hypoglycaemia.

Despite the above consensus, it remains unclear why these trials delivered such disparate and contradictory results. A possible explanation for the discordant findings of glycaemic control trials might relate to the high rate of use of total parenteral nutrition in the Leuven studies (Marik and Preiser 2010; Egi et al. 2011). Given that parenteral nutrition is uncommon in contemporary intensive care units, however, this possibility makes the Leuven studies of unclear modern significance. More importantly, and of relevance to this article, all these randomised studies considered diabetic and non-diabetic patients in the same cohort, and treated such patients in the same way, creating the potential for differing outcomes, because of the variable proportion of such patients and their pre-admission treatment. This uniform approach to glycaemic control in patients with or without diabetes mellitus (DM) may have stemmed from the notion that, even though pre-existing DM has been identified as a risk factor for the development of critical illness, patients with DM have comparable mortality rates to those without diabetes (Stegenga et al. 2010; Vincent et al. 2010), and no specific data existed at that time to suggest that they should be considered unique from the point of view of glycaemic management. Thus general ICU glycaemic control studies have until now influenced the management of glycaemia equally in DM and non-DM patients admitted to ICU. However, this may be unwise.

**Current Practice in Diabetic Patients**

Because of the above trials, current guidelines recommend targeting blood glucose levels of 140 to 180 mg/dl (7.8 to 10 mmol/L) in all critically ill patients (American Diabetes Association 2012; Ichai et al 2010). These recommendations appear justified not only by the findings of RCTs, but also by multiple observational studies that have demonstrated a higher mortality risk with both hyper- and hypo-glycaemia (Falciglia et al. 2009; NICE-SUGAR investigators 2012; Joeren et al. 2010). We speculate, however, that the ideal glycaemic range might differ in patients with DM, and moreover, even within such a cohort, it may depend on pre-existing glycaemic control. As DM patients comprise approximately 20% of all ICU admissions (Soulimane et al. 2012, Cely et al 2004), the issue of optimal glycaemic control in such patients appears clinically important.

It is important to reflect that in addition to patients with known diabetes, there are other patients admitted in ICU, who have chronic impairment in glycaemia (as shown by HbA1c levels), but in whom a diagnosis of diabetes had not been made prior to hospital presentation. Such patients with "unrecognised diabetes" at ICU admission may also require a specific level of glycaemic control similar to that of patients with known DM. To illustrate this point, in 2014 Plummer et al. described the prevalence of "unrecognised diabetes" in an Australian tertiary hospital as 5.5% of all ICU admissions (Plummer et al. 2014). However, an even higher value of 15% of ICU admissions was reported by a study conducted in Croatia (Gornik et al. 2010), and two American studies (Cely et al. 2004, Hoang et al. 2014) recorded "unrecognised diabetes" in 12% and 13.7 % of ICU admissions respectively. Thus patients with chronic hyperglycaemia (known diabetes and unrecognised diabetes) prior to ICU admission may represent up to 30% of all ICU admissions.

**Why Consider a Different Approach to Glycaemic Management Strategy in Diabetic Patients?**

**The Meaning of Hyperglycaemia**

Critically ill patients are at high risk of developing stress hyperglycaemia (Dungan et al. 2009), which is characterised by a high state of hepatic gluconeogenesis, excessive insulin resistance and increase of circulating cytokines, cortisol, epinephrine and glucagone. In patients with diabetes, chronic hyperglycaemia may already exist, and critically ill patients with DM may simply display slightly or moderately worse glucose derangements. Among non-diabetic patients, stress hyperglycaemia is associated with an increased risk of mortality after adjustment for illness severity. In particular the risk of death increases in proportion to blood glucose levels (Falciglia et al. 2009; Krinsley et al. 2003; Umpierrez et al. 2002; Finney et al. 2003). In contrast, data from several studies suggest that the adverse outcomes associated with hyperglycaemia are negligible or absent in patients with pre-existing diabetes (Sechterberger et al. 2013; Krinsley et al. 2013; Egi et al. 2008; Egi et al. 2011, Rady et al. 2005).

In all the studies cited above, a strong association between hyperglycaemia (episodes of hyperglycaemia and time-weighted hyperglycaemia) and ICU mortality was consistently found in non-diabetic patients but not in diabetic patients. This lack of association between hyperglycaemia and mortality may relate to the fact that diabetic patients have developed tolerance to hyperglycaemia. Thus diabetic patients may behave in relation to glucose the way patients with chronic obstructive pulmonary disease behave in relation to the correction of chronic hypoxaemia (Joosten et al. 2007), or patients with chronic hyponatraemia behave in relation to the correction of chronic hyponatraemia (Widdess-Walsh et al. 2007), and hypertensive patients relate to the rapid correction of high blood pressure levels (Shuaib et al.1992).

To further understand the importance of chronic hyperglycaemia in diabetic patients and its impact on acute glycaemic management, it is important to appreciate the value of measuring HbA1c. There is a direct relationship between HbA1c and mean glycaemia, because haemoglobin remains glycated during the approximate 120-day lifespan of the erythrocytes. As such a HbA1c of 6% corresponds to a mean plasma glucose level of 7.5 mmol/L (126 mg/dl) in the previous six to nine weeks, and each 1% increase in HbA1c corresponds to an increase of about 2mmol/L in mean plasma glucose levels (Peterson et al. 1998; Rohlfing et al. 2002). By measuring HbA1 in diabetic patients on admission, it is possible to estimate typical glucose levels, and theoretically it should then be possible to aim for type-individualised care (a kind of precision medicine) that seeks to maintain individual homeostasis by aiming for an acute glucose target, which approximates the normal glycaemic control for that diabetic patient prior to ICU admission.

To further understand this concept, Egi et al. (2011) evaluated in detail the interaction between pre-morbid hyperglycaemia, measured by means of HbA1c levels at ICU admission, acute glycaemia as delivered in ICU and hospital mortality. Their findings showed that patients with higher pre-admission HbA1c levels (>7%) were much less likely to die in hospital when their mean glucose concentrations in ICU were >180 mg/dl (10 mmol/L) (see Figure 1). These data support the concept that in the presence of chronic hyperglycaemia (Egi et al. 2011) tolerating higher than normal blood glucose levels can be considered safe and may even be potentially desirable in diabetic patients experiencing hyperglycaemia in the ICU.

In critically ill diabetic patients any consistent difference between premorbid glycaemia and mean glycaemia during ICU admission in the direction of decreased glucose levels could be considered a form of "relative hypoglycaemia". Thus if a patient is used to having, for example, a 180mg/dl (10 mmol/L) blood glucose level, then such a patient may experience the physiological stress of hypoglycaemia at 100 mg/dl (5.5 mmol/L) of blood glucose concentration. Such stress may then be the same as that of a normal person who develops a glucose level of <40 mg/dl (2.2 mmol/L). Such "relative hypoglycaemia" may be a silent contributor to morbidity and mortality in diabetic patients, especially in a context (ICU) where symptoms of "relative hypoglycaemia" are often masked by sedative or analgesic medication.

**The Importance of Hypoglycaemia**

Hypoglycaemia has deleterious effects in critically ill patients by increasing the systemic inflammatory response (Dotson et al 2008), inducing neuroglycopaenia (Schlenk et al. 2008), inhibiting the corticosteroid response to stress (Keller-Wood et al. 1983), impairing sympathetic system responsiveness (Herlein et al. 2006) and causing cerebral vasodilatation (Dieguez et al. 1997). Hypoglycaemia, both severe (<40 mg/dl or 2.2 mmol/L) and mild/ moderate (less than 70 mg/dl or 3.9 mmol/L), likely contributes to increased mortality in critically ill diabetics and non-diabetic patients. (Kalfon et al. 2015; NICE-SUGAR investigators 2012; Hermanides et al. 2010).

It seems biologically reasonable to think that hypoglycaemia during critical illness in diabetic patients should be considered in the context of chronic overall glycaemic control. The main aim in DM patients may then be not only to avoid absolute hypoglycaemia, but also to avoid "relative hypoglycaemia", which can be expressed by the "distance" or decrease between chronic glycaemia levels and the blood glucose levels experienced during acute illness. As described above, relative hypoglycaemic episodes for diabetic patients might have the same biological toxicity that absolute hypoglycaemic conditions produce in non-diabetic patients.

Moreover the 'protective' modifications associated with chronic hyperglycaemia leave cells vulnerable to relative glycopaenia, particularly in situations where hypotension and hypoxia co-exist. Some evidence suggests that chronic hyperglycaemia sets up a pattern of cellular conditions that might actually protect against acute hyperglycaemia-mediated damage but exacerbate hypoglycaemia-induced injury. One mechanism for this effect might be the preferential 'down regulation' of insulin independent glucose transporters under chronic hyperglycaemic conditions (Deane and Horowitz 2013).

**The Importance of Glycaemic Variability**

To define the best glycaemic management in diabetic patients, it is therefore logically necessary to take into account that it is relative dysglycaemia that may require treatment instead of just absolute hypoglycaemia or hyperglycaemia. Dysglycaemia can be seen to encompass three domains of glycaemic control: hypoglycaemia, hyperglycaemia and glycaemic variability. (Egi et al. 2007). Therefore a trend measure like glycaemic variability has been defined as the standard deviation of mean glucose level during ICU stay or as the difference between highest and lowest glycaemia in an established time period. Diabetic patients have greater absolute glycaemic variability than non-diabetic patients, and this might also affect the different association between glycaemia and outcome (Krinsley et al. 2009).

There is a growing body of evidence to suggest that for non-diabetic patients marked fluctuations in blood glucose are also related to an increased risk of mortality (Ali et al 2008; Meyfroidt et al. 2010; Krinsley et al. 2008; Dossett et al. 2008; Krinsley et al. 2009; Egi et al. 2006). A 2003 study found that in umbilical vein cells glycaemic fluctuations caused a higher level of oxidative stress compared to sustained hyperglycaemia (Quagliaro et al. 2003). This correlation has been demonstrated also in patients with type 2 diabetes. Such increased oxidative stress can result in endothelial dysfunction and can contribute to vascular damage (Monnier et al. 2006).

Despite these concerns, the impact of glycaemic variability in critically ill diabetic patients has not been extensively investigated. In fact, a large study demonstrated that glycaemic variability had an independent association with mortality among non-diabetic individuals but not among diabetics (Krinsley et al. 2009). Such a finding supports the concept that a degree of spontaneous tolerance to glycaemic variability may occur in diabetic patients due to their glycaemic history prior to ICU admission, which may have included chronic exposure to much greater levels of glycaemic variability than non-diabetic patients.

Thus efforts to maintain glycaemia in the normal range and decrease variability may be potentially injurious for patients with altered premorbid glycaemia. In this regard, a recent study demonstrated that a higher level of Time In Range glycaemia (TIR) (70mg/dl-140 mg/dl or 3.9-7.8 mmol/L) had a positive correlation with decreased mortality in a population of non-diabetic critically ill patients, while, among patients with diabetes, there was no consistent relationship between TIR and mortality (Krinsley et al. 2015).

**Chronic Glucose Management in Diabetes and its Relevance to Critical Illness**

Diabetes is mainly a chronic disease, and so lessons may also be derived from its "chronic" treatment, which have potential relevance to its acute management. For example, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study reported that in type 2 diabetic individuals in the ambulatory setting, aggressive glucose control to reduce glycosylated haemoglobin level from 8.3 to 6.4% over just a few months significantly *increased mortality* compared with control therapy. This means that a reduction of mean glycaemia of about 0.7 mmol/L per month appeared to be injurious. In contrast, the Action in Diabetes and Vascular Disease (ADVANCE study), published at the same time, showed that attempting to reduce glycosylated haemoglobin levels over a much longer period of time (slower decrease in glycaemia which allowed adaptation) was associated with a non-significant downward trend in mortality (Advance Collaborative Group et al. 2008; Gerstein et al. 2008; Dluhy et al. 2008 ).

There were important differences between ACCORD and ADVANCE in terms of blood glucose, which may be relevant to acute glycaemic management. Firstly, the baseline level of HbA1 was different: ACCORD included patients with a mean HbA1c of 8.1% compared with 7.5% in the ADVANCE study. Secondly, the speed of lowering HbA1c was very different: in the ACCORD study, the HbA1c levels fell to 6.7% within the

first 4 months while in ADVANCE the HbA1c decreased to 7% within the first 6 months (a big difference in speed of reduction - such that the rate of decrease in glycaemia was almost 10 times faster in ACCORD). These findings in the chronic setting, showing an association between increased mortality and fast reduction in HbA1c levels, raise concerns that any therapy that leads to a rapid decrease in glycaemia in diabetic patients with high premorbid HbA1c values is dangerous and should be avoided. As such, normalisation of glycaemia in ICU patients with DM and chronic hyperglycaemia may indeed be dangerous.

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**Conclusions**

On the basis of the modern "three domains" paradigm of glycaemic control in the acute setting, diabetic patients are different. In such patients, hyperglycaemia and greater glycaemic variability are not independently associated with increased mortality. Moreover the third domain of hypoglycaemia also appears different. In particular, in diabetic patients with poor pre-admission glycaemic control (chronic hyperglycaemia), even acute normoglycaemia may actually be a form of relative hypoglycaemia and may be associated with increased mortality. The evidence suggests that glycaemic management algorithms should be tailored differently for diabetic and non-diabetic patients and that a more liberal set of targets ("permissive moderate hyperglycaemia") may be justified in diabetic patients. Finally it appears desirable that further studies should investigate optimal blood glucose targets for critically ill diabetic patients in relation to premorbid glycaemia to test the feasibility and safety as well as the possible efficacy of a degree of "permissive moderate hyperglycaemia".

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