Stress-induced hyperglycaemia

ABSTRACT

Stress-induced hyperglycaemia is an important clinical entity. It is an adaptive immune-neurohormonal response to physiological stress in an attempt to increase metabolic substrates to struggling organs during a time of crisis. However, this acute hyperglycaemia is also responsible for a number of detrimental effects implying that treatment is necessary. Hence, admission hyperglycaemia is not necessarily equivalent to a diagnosis of diabetes mellitus but the blood glucose level needs to be interpreted in context of the patient's presenting complaint and previous glycaemic status. Stress-induced hyperglycaemia is associated with increased morbidity and short-term mortality. Thus prompt recognition of stress-induced hyperglycaemia and high risk hyperglycaemic patients with the stress hyperglycaemia ratio can help improve inpatient management. Patients with stress-induced hyperglycaemia who have recovered from their acute illness should be followed up as they remain at risk for incident diabetes. This review focuses on the definition, pathophysiology, targets, management and significance of stress-induced hyperglycaemia.

Stress-induced hyperglycaemia is defined as a transient hyperglycaemia associated with an acute illness (Dungan et al, 2009). Once the acute illness resolves, these patients regain normal glucose tolerance (Pakhetra et al, 2011). A diagnosis of stress-induced hyperglycaemia is usually reserved for patients without a history of diabetes mellitus (Dungan et al, 2009), but patients with diabetes can still have a stress-related hyperglycaemia response. Hence, stress-induced hyperglycaemia can be divided into two categories:

1. Hospital-related hyperglycaemia in patients without any evidence of prior diabetes. According to the American Diabetes Association and the American Association of Clinical Endocrinologists consensus, this is any blood glucose concentration of >7.8 mmol/litre in a patient without evidence of prior diabetes (Farrokhi et al, 2011; Corsino et al, 2017).
2. Stress-related hyperglycaemia in patients with pre-existing diabetes (Pakhetra et al, 2011). The definition of this category is not yet established, but Rau et al (2017) suggest that a blood glucose concentration of >13.9 mmol/litre is the cut-off level in defining stress-related hyperglycaemia in diabetic patients.

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In order to differentiate between newly diagnosed diabetes mellitus and stress-induced hyperglycaemia, guidelines used to recommend performing an oral glucose tolerance test shortly after discharge (Farrokhi et al, 2011; Corsino et al, 2017). However, the use of glycated haemoglobin (HbA_{1c}) is now preferred as it allows clinicians to differentiate between stress-induced hyperglycaemia and previously undiagnosed diabetes (Farrokhi et al, 2011). HbA_{1c} is characterized by decreased biological variability and hence is relatively unaffected by an acute stress response, making it ideal in this situation. Nevertheless, an issue remains: an HbA_{1c} level of >6.5% is used to diagnose patients with diabetes, although this only identifies two-thirds of patients compared to diagnosing patients using fasting blood glucose level (Farrokhi et al, 2011). The above mentioned categories are summarized in *Figure 1*.

Pathophysiology of stress-induced hyperglycaemia

Sepsis, trauma, burns or any other form of acute illness threaten the normal homeostatic processes of the body (Farrokhi et al, 2011). This is perceived as stress and leads to activation of the hypothalamic–pituitary–adrenal axis and the sympathetic autonomic nervous system (Marik and Bellomo, 2013).

Stress leads to hypercortisolaemia which promotes hepatic gluconeogenesis and glycogenolysis (Kajbaf et al, 2007). Cortisol also enhances transcription of the phosphoenolpyruvate carboxykinase (PEPCK) gene (Kajbaf et al, 2007) which is involved in gluconeogenesis from non-carbohydrate sources such as lactate, alanine and pyruvate. In addition, hypercortisolaemia leads to increased levels of circulating amino acids as a result of increased protein catabolism. These circulating amino acids serve as precursors for gluconeogenesis via the PEPCK enzyme.

Stress also leads to increased secretion of pro-inflammatory cytokines including tumour necrosis factor-alpha (TNF-α), interleukin-1 (IL-1) and interleukin-6 (IL-6) (Kajbaf et al, 2007). These increase insulin resistance by interfering with the insulin signalling pathway (Corsino et al, 2017), for example TNF-α activates c-Jun N-terminal kinase. Once activated, this signalling protein phosphorylates and inactivates insulin receptor substrate-1. This interrupts the insulin signalling pathway and hence leads to increased insulin resistance and reduced peripheral glucose utilization (Kajbaf et al, 2007).

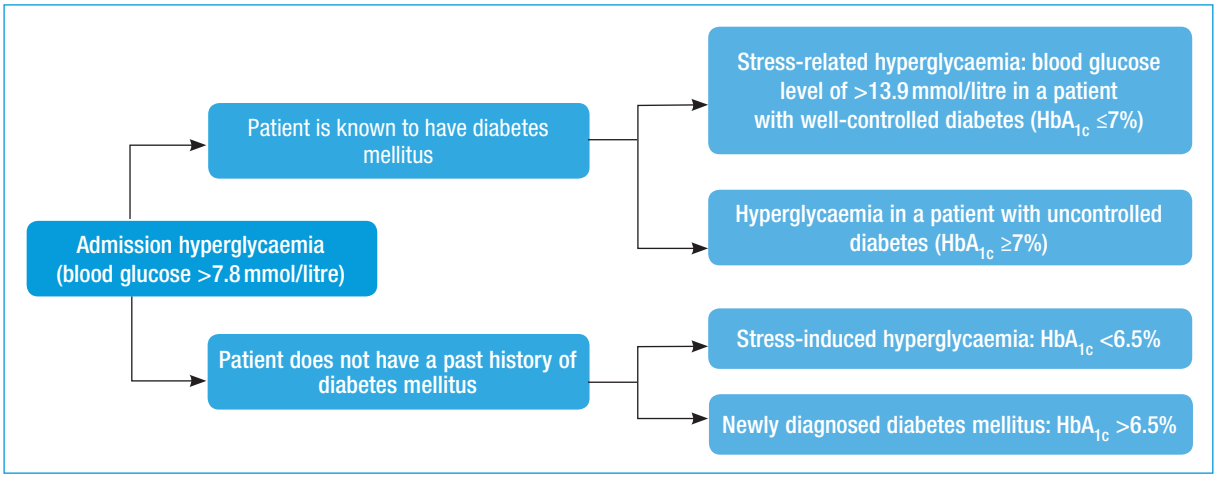

Figure 1. Flow diagram summarizing the classification of admission hyperglycaemia. HbA_{1c} = glycated haemoglobin.

Pro-inflammatory cytokines also reduce the expression of peripheral growth hormone receptors and the level of growth hormone binding protein (Vanhorebeek and van den Berghe, 2006), reducing hepatic and peripheral tissue sensitivity to growth hormone. Hence, insulin-like growth factor (IGF)-1 and IGF binding protein-3 secretion is reduced, resulting in cessation of the anabolic activities of growth hormone (Ross et al, 1991; Baxter, 2001; Vanhorebeek and van den Berghe, 2006). This reduced sensitivity to growth hormone stimulates further growth hormone secretion through positive feedback. The increased growth hormone secretion that occurs in this setting is not pulsatile (Ross et al, 1991; Baxter, 2001). This is important as usually insulin-like growth factor-1 is secreted in response to growth hormone pulses (Baxter, 2001). Hence with reduced hepatic sensitivity and loss of the pulsatile pattern of growth hormone secretion, insulin-like growth factor-1 secretion and its activities are impaired.

The increased levels of growth hormone secreted lead to increased lipolysis, generating free fatty acids and glycerol. Glycerol also serves as a substrate for gluconeogenesis. Growth hormone also opposes the effects of insulin on the peripheral tissues by uncoupling the insulin-stimulated phosphatidylinositol 3-kinase from its downstream effects (Takano et al, 2001), leading to increased insulin resistance and hyperglycaemia (Rizza et al, 1982).

Hyperglycaemia also promotes cytokine release from monocytes and macrophages (Kajbaf et al, 2007). TNF-α, IL-1 and IL-6 provide positive feedback to the hypothalamic–pituitary–adrenal axis, as they promote secretion of corticotrophin-releasing hormone from the paraventricular nucleus (Marik and Bellomo, 2013).

Adrenaline and noradrenaline release during stress promotes glucagon secretion (Sorenson et al, 1979; Gromada et al, 1997). Adrenaline inhibits insulin release from the pancreas and leads to insulin deficiency (Farrokhi et al, 2011; Corsino et al, 2017). The catecholamines also motivate PEPCK gene transcription promoting gluconeogenesis via glucagon (Kajbaf et al, 2007).

Stress leads to insulin resistance, insulin deficiency, increased hepatic glucose production and release, and reduced peripheral glucose utilization. If the pancreas is unable to compensate by increasing insulin production and release, the net effect is hyperglycaemia. Moreover, hyperglycaemia desensitizes pancreatic beta-cells, and this results in impaired insulin release and promotes further hyperglycaemia (Farrokhi et al, 2011). Hyperglycaemia reinforces the above processes by stimulating further inflammatory cytokine release, leading to a vicious cycle.

Is this hyperglycaemia beneficial or detrimental?

Whether stress-induced hyperglycaemia is beneficial or detrimental is controversial. Some beneficial effects of acute hyperglycaemia include the following:

1. Glucose is mostly used by tissues that are non-insulin dependent, e.g. CNS, white and red blood cells, and the reticulo-endothelial system. In stress-induced hyperglycaemia, insulin resistance leads to reduced translocation of GLUT 4 transporters from intracellular stores to the cell membrane. This reduces glucose uptake by peripheral and non-essential tissues. For example, in sepsis, increased GLUT 1 RNA transcription is seen in the CNS and the macrophages. Thus in addition to creating a new glucose balance, stress-induced hyperglycaemia causes a preferential uptake of glucose across its concentration gradient into the CNS cells and macrophages via GLUT 1 transporters (Marik and Bellomo, 2013).
2. Glucose is the primary metabolic substrate for macrophages. Hence stress-induced hyperglycaemia allows increased glucose influx into these cells which, when metabolized via the pentose pathway, leads to the metabolic intermediates required for nicotinamide adenine dinucleotide phosphate (NADPH) generation (used by immune cells to generate free radicals) (Marik and Bellomo, 2013).
3. Acute hyperglycaemia may protect against cell death by promoting anti-apoptotic pathways and promoting angiogenesis (Marik and Bellomo, 2013).

> Insulin also has cardioprotective effects by increasing the release of nitric oxide via activation of endothelial nitric oxide synthase in platelets and the endothelium.

Based on the above, acute stress-induced hyperglycaemia is protective and serves as an adaptive response to insults. The immune-neuroendocrine systems free up and provide metabolic fuel substrates for the immune system, CNS and other struggling organs during periods of stress. Hence iatrogenic normalization of this process may impair cerebral and immune system functioning during a time of crisis (Marik and Bellomo, 2013).

However, acute hyperglycaemia has a number of detrimental effects including the following:

1. Glucose is a pro-inflammatory mediator (Kajbaf et al, 2007). It increases and enhances transcription factors (intra-nuclear NFκB, activator protein-1 and growth factor) that regulate genes which encode pro-inflammatory mediators. This promotes further inflammatory cytokine production and promotes the inflammatory process (Kajbaf et al, 2007).
2. Glucose promotes insulin resistance via overexpression of c-Jun N-terminal kinase (Kajbaf et al, 2007).
3. Acute hyperglycaemia diminishes endothelial nitric oxide, causing organ hypoperfusion secondary to vasoconstriction (Kajbaf et al, 2007). Furthermore, nitric oxide is also used up by binding to superoxide radicals generated by the immune cells. When nitric oxide and these superoxide radicals bind, they generate peroxynitrite which enhances platelet aggregation, thrombotic events and diminishes mitochondrial function (Kajbaf et al, 2007).
4. Hyperglycaemia increases the risk of infections (Kajbaf et al, 2007). The increased glucose influx into immune cells leads to glucotoxicity. Moreover, hyperglycaemia also impairs neutrophil function, promotes lymphocyte apoptosis and suppresses proliferation of T cells. The hyperglycaemic state leads to glycosylation of immunoglobulins and complements, diminishing their effect (Matias et al, 2013).

Thus stress-induced hyperglycaemia has both beneficial and detrimental effects, but it is unclear at what point this hyperglycaemia becomes adverse. A review by Marik and Bellomo (2013) suggested that the duration and severity of hyperglycaemia is important in determining whether it is beneficial or detrimental. Animal experimental studies by Xu et al (2004) and Ma et al (2006) demonstrated that acute hyperglycaemia (<2–4 weeks) is beneficial while chronic hyperglycaemia (>6 weeks) becomes deleterious. In addition, it is possible that severe stress hyperglycaemia, i.e. blood glucose level of >12.2 mmol/litre, may be harmful. This may be related to increased serum osmolality promoting fluid shifts from the intracellular compartment to the extracellular compartment. Furthermore, severe hyperglycaemia exceeds the renal threshold, resulting in an osmotic diuresis which may eventually lead to hypovolaemia (Marik and Bellomo, 2013).

Benefits of insulin therapy

Insulin reverses almost all of the undesirable effects of acute hyperglycaemia (Kajbaf et al, 2007).

Insulin has anti-inflammatory effects by inhibiting the pro-inflammatory actions of glucose (Kajbaf et al, 2007). Furthermore, insulin reduces inducible nitric oxide synthase expression, limiting the amount of nitric oxide produced during oxidative stress. This is beneficial since reducing the intracellular concentration of nitric oxide leads to less peroxynitrite being formed and mitochondrial function is preserved, preventing glucotoxicity (Kajbaf et al, 2007).

Insulin also has cardioprotective effects by increasing the release of nitric oxide via activation of endothelial nitric oxide synthase in platelets and the endothelium, promoting vasodilatation and inhibition of platelet aggregation (Kajbaf et al, 2007).

Glycaemic targets in critical care settings

The glycaemic targets depend on whether the patient is in an intensive therapy unit or a non-intensive therapy unit setting.

Glucose control in intensive therapy unit patients should be between 7.8 and 10 mmol/litre. However, more stringent targets, e.g. 6.1–7.8 mmol/litre, may be appropriate for selected patients if achievable without significant risk of hypoglycaemia (Farrokhi et al, 2011).

These targets were based on a number of trials of glycaemic control in intensive therapy unit populations. The Leuven intensive insulin therapy trial (van den Berghe et al, 2001), and the intensive insulin therapy trial in the medical intensive care unit by van den Berghe et al (2006), revealed that intensive insulin therapy targeting serum glucose levels between 4.4 and 6.1 mmol/litre resulted in less intensive therapy unit and total hospital complications in both surgical and medical, diabetic and non-diabetic patients (van den Berghe et al, 2001, 2006). However, these low glucose levels were difficult to achieve without increasing the risk of severe hypoglycaemia (De La Rosa et al, 2008).

The Glucontrol trial (Preiser et al, 2009) did not find any difference in mortality between intensive (4.4–6.1 mmol/litre) and conventional (7.8–10.0 mmol/litre) glucose control in randomized surgical and medical, diabetic and non-diabetic patients in the intensive therapy unit setting. The NICE-SUGAR trial (NICE-SUGAR Study Investigators et al, 2009, 2012) also reported no difference in hospital mortality but found increased mortality at 90 days' follow up in the intensive glycaemic control group compared to the conventional glycaemic control group (27.5% *vs* 24.9%) (NICE-SUGAR Study Investigators et al, 2009). Subsequent analysis found a higher frequency of hypoglycaemia in the intensive glycaemic control group (6.9% *vs* 0.5%) and those with hypoglycaemia had a two-

fold increased mortality compared to patients without hypoglycaemia (NICE-SUGAR Study Investigators et al, 2012). The NICE-SUGAR trial's population also consisted of diabetic and non-diabetic patients.

Interestingly, a 2011 study conducted in an intensive therapy unit setting revealed that patients with uncontrolled diabetes (HbA_{1c} >7%) had reduced mortality rates when hyperglycaemia was present compared to non-diabetic and controlled diabetic (HbA_{1c} <7%) patients with inpatient hyperglycaemia (Egi et al, 2011).

In the non-intensive therapy unit setting, glycaemic targets are similar, aiming for pre-meal glucose levels <7.8 mmol/litre with random blood glucose levels <10 mmol/litre (Corsino et al, 2017). In patients with terminal illness, limited life expectancy or high risk of hypoglycaemia less stringent glycaemic targets (<11.1 mmol/litre) may be appropriate (Corsino et al, 2017). There are no large studies to determine if improved glycaemic control in the non-intensive therapy unit setting results in reduced morbidity and mortality. However, a randomized control trial and a meta-analysis in 2011 reported that improved glucose control may reduce hospital complications in general surgery patients (Umpierrez et al, 2011).

Management

In the intensive therapy unit setting, intravenous insulin is the best approach to control hyperglycaemia (Corsino et al, 2017). Intravenously administered insulin is effective, has few contraindications and its short half life allows flexibility in the event of unpredicted changes in the patient's nutrition, medications and health (Corsino et al, 2017). An intravenous insulin infusion should be commenced when serum glucose levels are above 10 mmol/litre (Corsino et al, 2017). There are various protocols that can be used but it is vital that nursing staff are comfortable with the protocol being used and that hourly glucose monitoring can be performed at least until euglycaemia is achieved (thereafter glucose levels can be checked 2–3-hourly) (Corsino et al, 2017). *Table 1* shows a variable rate intravenous insulin infusion protocol as per the Joint British Diabetes Societies for Inpatient Care Group (2014) guidelines.

In a non-intensive therapy unit setting, patients with blood glucose levels of more than 7.8 mmol/litre without a prior history of diabetes should have bedside point of care glucose testing for at least 24–48 hours (Umpierrez et al, 2012). If the glucose levels are persistently higher than 7.8 mmol/litre, therapeutic intervention will be indicated (Umpierrez et al, 2012).

Subcutaneous insulin is recommended as the preferred approach to control hyperglycaemia in the non-intensive therapy unit setting (Dungan et al, 2009; Corsino et al, 2017). However, critically ill patients in a non-intensive therapy unit setting should still be managed with intravenous insulin therapy for the reasons mentioned earlier. Hence subcutaneous insulin is preferred in patients with either newly recognized hyperglycaemia or type 2 diabetes mellitus who are not critically ill.

Table 1. Prescribing a variable rate intravenous insulin infusion as per the Joint British Diabetes Societies for Inpatient Care Group guidelines

	Insulin rates (ml/hr)		
Glucose (mmol/litre)	**Reduced rate**	**Standard rate**	**Increased rate**
<4.0	0	0	0
4.1–8.0	0.5	1	2
8.1–12.0	1	2	4
12.1–16.0	2	4	6
16.1–20.0	3	5	7
20.1–24.0	4	6	8
>24.1	6	8	10

Most patients should be prescribed the standard rate, but patients with insulin sensitivity or insulin resistance may require the reduced rate or the increased rate respectively (Joint British Diabetes Societies for Inpatient Care Group, 2014)

The preferred subcutaneous insulin regimen for glycaemic management is the basal-bolus regimen in combination with a correction insulin scale (Dungan et al, 2009; Corsino et al, 2017). This regimen is considered the most physiological approach as it covers the main components of insulin requirements:

1. Basal – what is necessary in the fasting state
2. Nutritional – what is required following meals
3. Supplemental – what is necessary for unexpected glucose elevations (Corsino et al, 2017).

Several studies have shown that basal-bolus insulin regimens are more beneficial than a sliding scale in patients with type 2 diabetes (Moghissi et al, 2009; Corsino et al, 2017). There are better glucose control results together with reduced risk of undesirable levels of hypoglycaemia (Corsino et al, 2017).

A 2012 Endocine Society clinical practice guideline also highlighted that scheduled basal-bolus insulin is safe in non-critically ill hospitalized patients with either newly recognized hyperglycaemia or with type 2 diabetes (Umpierrez et al, 2012).

Another regimen that was analysed in type 2 diabetics was the basal-plus regimen. This involves a daily dose of basal insulin and correction doses with a rapid-acting insulin analogue given by a sliding scale. This was also noted to achieve good glycaemic control and similar hypoglycaemia rates to the basal-bolus regimen. The basal-plus regimen may be an alternative to the basal-bolus regimen in insulin- naive patients or those with reduced calorie intake (Corsino et al, 2017). In fact, the 2012 Endocrine Society clinical practice guideline states that nil by mouth patients can receive the basal insulin daily dose (Umpierrez et al, 2012).

Thus, evidence supports the use of the basal-bolus or basal-plus regimen in patients with type 2 diabetes who are not critically ill, even those who are treated on diet alone,

KEY POINTS

- Stress-induced hyperglycaemia is defined as a transient hyperglycaemia associated with an acute illness.
- Insulin reverses almost all of the undesirable effects of acute hyperglycaemia.
- Stress-induced hyperglycaemia in critically ill patients in either an intensive care or non-intensive care setting with blood glucose readings of >10 mmol/litre should be managed using intravenous insulin therapy aiming for blood glucose levels of 7.8–10 mmol/litre.
- Stress-induced hyperglycaemia in non-critically ill patients is best managed with subcutaneous insulin using a basal-bolus regimen in newly diagnosed hyperglycaemic patients and a basal-bolus or a basal-plus regimen in non-critically ill type 2 diabetic patients.
- Patients with stress-induced hyperglycaemia who recover from the acute illness need to be followed up as they remain at high risk of incident diabetes.

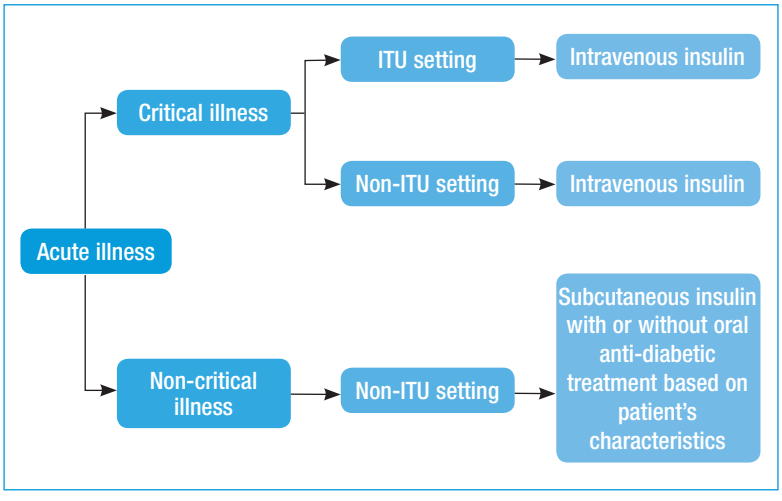

Figure 2. Algorithm for the management of stress-induced hyperglycaemia. ITU = intensive therapy unit.

oral antidiabetic agents or low dose insulin (<0.4 units/kg/day) and the basal-bolus regimen in non-critically-ill patients with newly recognized hyperglycaemia (Umpierrez et al, 2012; Corsino et al, 2017).

The recommended total daily insulin dose for most patients should start at 0.3–0.5 units/kg/day. Elderly patients and those with renal impairment need lower initial daily doses (<0.3 units/kg/day) (Corsino et al, 2017).

Oral antidiabetic agents use was not recommended in previous guidelines, but there is increasing evidence for treatment with dipeptidyl peptidase-4 inhibitors alone or in combination with insulin (Corsino et al, 2017).

Sulfonylureas are best avoided in view of the risk of causing severe and prolonged hypoglycaemia, especially in patients with chronic kidney disease and the elderly (Farrokhi et al, 2011). Metformin is also often discontinued in view of renal insufficiency (Farrokhi et al, 2011). However, the use of metformin is seeing a resurgence among certain patients as the risk of hypoglycaemia is lower provided that renal function is still preserved (Silva-Perez et al, 2017).

A crucial component that tends to be overlooked in these patients is nutrition. These patients need to be assessed individually and have proper meal planning in order to provide enough calories to meet the metabolic demands while trying to optimize glycaemic control (Umpierrez et al, 2012). The management of stress-induced hyperglycaemia is summarized in *Figure 2*.

Before discharge patients on intravenous insulin need to be switched to subcutaneous insulin and their blood glucose levels monitored. Stress-induced hyperglycaemia in patients with an HbA_{1c} <6.5% should resolve and these patients may usually be discharged on no antidiabetic treatment if their blood glucose levels are satisfactory, but patients with elevated HbA_{1c} levels need treatment (Farrokhi et al, 2011).

Significance of stress-induced hyperglycaemia

In-hospital hyperglycaemia is an important marker of poor clinical outcome and is associated with a higher mortality (Roberts et al, 2015). Admission hyperglycaemia is a biomarker of critical illness, but a better biomarker of critical illness is the stress hyperglycaemia ratio (calculated as the admission glucose level divided by the A_{1c}-derived estimated average glucose) (Roberts et al, 2015; Rau et al, 2017). The stress hyperglycaemia ratio controls for the individual patient's background hyperglycaemia, and is an independent predictor of critical illness in patients across the glycaemic spectrum (Roberts et al, 2015). Stress hyperglycaemia ratio can identify patients with relative hyperglycaemia as high risk for critical illness below the usual hospital threshold for glucose lowering therapy, e.g. <10 mmol/litre (Roberts et al, 2015).

Stress hyperglycaemia ratio = (admission hyperglycaemia (mmol/litre))/(A_{1c}-derived estimated average glucose)

where A_{1c}-derived estimated average glucose (mmol/litre)=((28.7×HbA_{1c} (%))-46.7)/18

Apart from the short-term association of risk of critical illness, studies suggest that stress-induced hyperglycaemia identifies patients at subsequent risk of incident type 2 diabetes. A study by Plummer et al (2016) revealed that stress-induced hyperglycaemia appears to approximately double the risk of incident diabetes in survivors of critical illness especially in middle-aged patients. Hence, patients with stress-induced hyperglycaemia have to be followed up as 60% of patients admitted with new hyperglycaemia were confirmed to be diabetic at 1 year (Corsino et al, 2017).

Conclusions

Stress-induced hyperglycaemia is a state of temporary insulin resistance and concomitant insulin deficiency (Ali Abdelhamid et al, 2016). This transient hyperglycaemia is associated with a higher short-term mortality (Ali Abdelhamid et al, 2016), so regular blood glucose monitoring is important in acutely ill patients to detect

stress-induced hyperglycaemia. If glucose levels are elevated, HbA_{1c} should also be checked in order to determine the patient's previous glycaemic status in both diabetic and non-diabetic patients. This will help guide management and determine the stress hyperglycaemia ratio. Stress-induced hyperglycaemia is also associated with a greater risk of incident diabetes and hence these patients' glycaemic status needs to be followed up after discharge (Plummer et al, 2016; Corsino et al, 2017). **BJHM**

Conflict of interest: none.

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