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Stress hyperglycaemia

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Abstract

Results of randomised controlled trials of tight glycaemic control in hospital inpatients might vary with population and disease state. Individualised therapy for different hospital inpatient populations and identification of patients at risk of hyperglycaemia might be needed. One risk factor that has received much attention is the presence of pre-existing diabetes. So-called stress hyperglycaemia is usually defined as hyperglycaemia resolving spontaneously after dissipation of acute illness. The term generally refers to patients without known diabetes, although patients with diabetes might also develop stress hyperglycaemia—a fact overlooked in many studies comparing hospital inpatients with or without diabetes. Investigators of several studies have suggested that patients with stress hyperglycaemia are at higher risk of adverse consequences than are those with pre-existing diabetes. We describe classification of stress hyperglycaemia, mechanisms of harm, and management strategies.

Introduction

Transient hyperglycaemia during severe illness in adult patients without known diabetes was thought to be harmless or even advantageous. However, results of a large randomised controlled trial¹ showed clear mortality benefits from intensive insulin therapy for patients in intensive care units (ICUs), irrespective of whether a previous diagnosis of diabetes had been made. Subsequent reports^{2–8} in mixed medical and surgical ICUs have tempered initial enthusiasm for strict glycaemic control, mainly because of an unacceptable risk of hypoglycaemia. Such findings have triggered appeals for focused efforts to identify patients who are at high risk of hyperglycaemia-mediated harm and likely to benefit from interventions.⁹

Investigators of several studies suggest that patients with stress hyperglycaemia and no previous diagnosis of diabetes face worse consequences at a given severity of hyperglycaemia than do those with pre-existing diabetes. We describe challenges in identification and diagnosis of such patients, analyse the evidence that lends support to the harms of stress hyperglycaemia, review the unique causal features and proposed

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Contributors

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Conflicts of interest

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mechanisms of harm of stress hyperglycaemia, suggest management strategies, and identify areas of future study. We intend not to diminish the importance of pre-existing diabetes or chronic glycaemic control, but to draw attention to the adverse consequences or concomitant effects of acute hyperglycaemia.

Diagnosis

Stress hyperglycaemia generally refers to transient hyperglycaemia during illness and is usually restricted to patients without previous evidence of diabetes. For the purpose of this Seminar, we will discuss physical—rather than psychological—stress. However, the identification of such patients is complex. No guidelines specifically define stress hyperglycaemia. In a technical review written by the Diabetes in Hospitals Writing Committee of the American Diabetes Association (ADA),¹⁰ patients are classified into one of three groups—known diabetes, newly diagnosed diabetes, and hospital-related hyperglycaemia (panel). This classification needs information from hospital follow-up that is not usually available. Change in glucose from baseline and not the absolute glucose concentration might be of value, irrespective of whether a patient has pre-existing diabetes (figure 1). Thus, we propose two diagnostic categories of stress hyperglycaemia—hospital-related hyperglycaemia according to the ADA consensus definition (fasting glucose >6.9 mmol/L or random glucose >11.1 mmol/L without evidence of previous diabetes), and pre-existing diabetes with deterioration of preillness glycaemic control. The most appropriate cutoff point for stress hyperglycaemia in patients with pre-existing diabetes needs to be established, but certainly a patient with a well controlled ($<7\%$) glycosylated haemoglobin (HbA_{1c}) whose glucose concentration is consistently higher than the threshold defined for hospital-related hyperglycaemia would qualify.

30% of people who have diabetes in the USA are unaware of their status¹¹ and, therefore, many hospital inpatients with apparent stress hyperglycaemia have underlying diabetes or prediabetes (table).^{12–18} In an undifferentiated hospital population, results from a small study¹⁸ showed that 60% of patients with admission hyperglycaemia had confirmed diabetes at 1 year. Another study showed that nearly one in five adult inpatients had probable unrecognised diabetes—identified by an admission HbA_{1c} higher than 6.1%.¹⁹ In this study, random glucose concentrations poorly predicted elevated HbA_{1c} , indicating the need for more sophisticated diagnostic criteria than are available.

Epidemiology

Poor outcomes related to stress hyperglycaemia

Researchers of intravenous insulin therapy have not specifically compared patients with and without stress hyperglycaemia in prospective controlled studies.^{1–6} Other investigators²⁰ exclude patients without known diabetes altogether. With the exception of a few randomised trials, most data are observational and drawn from ICUs or patients with acute myocardial or cerebrovascular events. One retrospective review²¹ of 1886 unselected hospital inpatients was stratified according to whether patients had normoglycaemia, pre-existing diabetes, or newly diagnosed hyperglycaemia (fasting glucose >7 mmol/L or random glucose >11.1 mmol/L on two separate occasions). Compared with patients with normoglycaemia, after adjustment for age, body-mass index, sex, hyper tension, coronary artery disease, infection, renal failure, and ICU admission, mortality was 18.3 times higher in patients with newly diagnosed hyperglycaemia ($p<0.05$), but only 2.7 times higher in those with known diabetes ($p<0.05$). This study did not distinguish between a new diagnosis of diabetes and transient stress hyperglycaemia.

However, a relation between short-term glycaemic control and hospital outcomes has been identified.¹⁹ Patients with hyperglycaemia without known diabetes who were critically ill^{22–26} or had acute coronary or cerebro-vascular^{1,13,27–32} events were shown to have increased risk of mortality, although patients who were hyperglycaemic with known diabetes did not. Increased mortality was also reported in hyperglycaemic inpatients with or without diabetes who had acute myocardial infarction or acute coronary syndrome,^{33–40} or cerebrovascular accident.⁴¹ Other studies^{41–45} reported no rise in risk related to hyperglycaemia in inpatients in ICUs, or in patients with acute coronary syndrome, or cerebrovascular accident.

Stress hyperglycaemia in ICUs

In posthoc analysis, data from a large randomised controlled trial⁴⁶ of intensive insulin therapy in a surgical ICU suggest that patients with a previous diagnosis of diabetes were at lower risk of mortality than were those without or newly diagnosed with diabetes (odds ratio [OR] 0.356, 95% CI 0.158–0.803, $p=0.01$). Posthoc analysis of the counterpart to this study in a medical ICU showed a reduction in mortality only in patients needing an ICU stay of 3 days or longer, and seemingly only in patients with newly discovered hyperglycaemia (11.5% reduction in mortality in patients with new hyperglycaemia vs 1.8% increase in mortality with those with known diabetes).² In a pooled analysis of both trials, patients with diabetes achieved no survival benefit, although the number of patients with known diabetes was small.²²

In other randomised studies,^{3,6,8} results were stratified according to the presence of pre-existing diabetes. Investigators of a small ($n=523$)⁶ single-centre study reported no benefit of intensive intravenous insulin therapy with a mean glucose target of 4.4–6.1 mmol/L compared with a target of 10–11.1 mmol/L. This study was powered to detect an 8% absolute risk reduction. No difference in outcomes between patients with or without diabetes was identified. Investigators of a multicentre randomised controlled study of patients with sepsis noted outcomes did not differ between those with or without diabetes treated with intensive insulin therapy. However, this study was stopped before enrolment was completed largely because of frequent hypoglycaemia.³

A pivotal, large, multicentre randomised controlled trial (NICE-SUGAR)⁸ comparing conventional (<10 mmol/L) versus tight (4.5–6.0 mmol/L) glycaemic control using intravenous insulin infusions in ICU patients showed increased mortality for patients in the intensive arm (OR 1.14, 95% CI 1.02–1.28, $p=0.02$). The treatment effect did not differ between surgical and non-surgical patients, nor was a difference observed between patients with or without known diabetes.

Other non-randomised or observational studies provide less robust data than does the NICE-SUGAR trial, but deserve mention because they attempt to identify patients with stress hyperglycaemia. In a mixed surgical ($n=676$), medical ($n=1856$), and trauma ($n=134$) ICU, outcomes in patients with diabetes ($n=532$) were compared with those in patients without known diabetes after implementation of a moderately tight glycaemic control protocol (target blood glucose concentrations 6.9 mmol/L).⁴² Mortality was significantly reduced in non-diabetic patients but not in those with known diabetes. Furthermore, in patients without diabetes, mortality began to rise when mean glucose concentration exceeded 7.8 mmol/L in patients without diabetes, whereas in patients with diabetes this threshold was 10 mmol/L.

Several observational studies have assessed whether patients with stress hyperglycaemia have a high risk of poor outcomes. A large observational study of 728 patients with diabetes and 4218 patients without diabetes established that at any mean ICU glucose concentration, ICU (but not hospital) mortality is greater (up to nearly four times) in patients without

diabetes than in those with the disorder,²³ even after adjustment for disease severity (Acute Physiology and Chronic Health Evaluation II score). In a mixed ICU sample of 2826 patients, those without diabetes who needed treatment for hyperglycaemia had higher sequential organ failure assessment (SOFA) scores, greater hospital length of stay (8.0 vs 6.7 days, $p<0.001$), and higher mortality rates (10% vs 6%, $p<0.01$) than did patients with known diabetes, despite lower median glucose and adjustment for severity of illness and other covariates.²⁴ By contrast, patients with the disorder had the same death rate as normoglycaemic non-diabetic patients (6% vs 5%), despite higher SOFA scores and median glucose values. The high mortality rate in hyperglycaemic patients without known diabetes and absence of relation of hyperglycaemia to mortality in patients with diabetes was also reported in mixed ICU populations²⁵ and in those with severe sepsis.²⁶ However, not all results from ICU studies show a high risk of mortality related to acute hyperglycaemia.⁴³

Cardiovascular disease and stroke

The relation between newly discovered hyperglycaemia and mortality in patients presenting with acute myocardial infarction or acute coronary syndrome has been investigated. Unfortunately, most studies rely on glucose concentrations at admission to identify stress hyperglycaemia. In a meta-analysis,⁴⁷ the pooled unadjusted relative risk (RR) of in-hospital mortality after myocardial infarction in 1856 patients without diabetes who had stress hyperglycaemia at admission was 3.9 (95% CI 2.9–5.4) compared with normoglycaemic non-diabetic patients. By comparison, the risk of death in 688 hyperglycaemic patients with diabetes was 1.7 (95% CI 1.2–2.4) relative to normoglycaemic patient with diabetes.

Other studies support these findings. In more than 160 000 patients admitted with acute myocardial infarction, glucose concentration at admission was associated with a steep rise in 30-day mortality for those without known diabetes: for glucose concentrations of 6.1–7.8 mmol/L on admission, OR 1.17, (95% CI 1.11–1.24); 13.3 mmol/L or more, OR 1.87, (95% CI 1.75–2.00).⁴⁸ However, for patients with established diabetes, mortality rose only at the highest glucose concentration (>13.3 mmol/L OR 1.32, 95% CI 1.17–1.50). Discrepancies between studies might be explained in part by the length of follow-up—the association between diabetes status and mortality strengthened as the length of follow-up increased. With longer follow-up, the association between diabetes and mortality was significant, but the association with stress hyperglycaemia became non-significant.^{33,34}

Another study²⁶ investigated the role of acute and chronic hyperglycaemia in 827 patients with diabetes, 324 of whom had at least two HbA_{1c} measurements in the previous 2 years. Glucose concentrations at admission in the third (2.84 mmol/L, 95% CI 1.04–7.76, $p=0.04$) or fourth (5.03 mmol/L, 95% CI 1.90–13.26, $p=0.001$) quartiles independently predicted in-hospital mortality after acute myocardial infarction. However, mortality did not differ much between quartiles of HbA_{1c}. Results of another study⁴⁹ confirmed no association between mortality and HbA_{1c}, thus drawing attention to the potential importance of acute hyperglycaemia over chronic hyperglycaemia in hospital inpatients with acute myocardial infarction.

A retrospective analysis⁵⁰ of 433 patients after stroke established that blood glucose concentrations higher than 10 mmol/L at admission (OR=2.1, 95% CI 1.1–4.6, $p=0.02$), but not diabetes itself, was an independent predictor of dependency 1 year after first-ever stroke. A meta-analysis⁵¹ showed that in patients without diabetes, stress hyperglycaemia (definition varied by study) was associated with a high risk of mortality after stroke (pooled RR 3.07, 95% CI 2.50–3.79). However, this was not true for patients with diabetes (pooled RR 1.30, 95% CI 0.49–3.43). In further studies,^{31,32,52} Glucose concentration on admission was associated with higher mortality rates in patients without a history of diabetes than in

those with a history of diabetes—both for ischaemic stroke and intracranial haemorrhage. This finding was not confirmed in another study.⁴⁵

In a prospective observational analysis⁴³ of 262 patients with stroke, researchers used a normal fructosamine and to identify those with transient hyperglycaemia. HbA_{1c} Patients with transient hyperglycaemia had worse stroke severity scores than did those with either known diabetes or normoglycaemia. Furthermore, 30-day mortality was higher in patients with transient hyperglycaemia than in those with normoglycaemia (27.4% vs 12.7%, $p=0.01$), but no significant difference between patients with diabetes (16.2%) and normoglycaemia was reported.

Surgery

The first Leuven study¹ consisted largely of postsurgical patients, two-thirds of whom had cardio thoracic surgery. Because patients with no history of diabetes benefited most from intensive insulin therapy, the same could be true for the subset of post cardiothoracic surgery patients. However, a prospective study²⁰ with historical controls showed reductions in mortality, hospital length of stay, and surgical site infections after cardiothoracic surgery in patients with diabetes who received intensive insulin therapy. By contrast with the Leuven study, in the Furnary study⁵³ patients with transient hyperglycaemia were excluded, indicating that patients with diabetes also benefit from glycaemic control. This finding seems to be in agreement with another study.⁵⁴

Chronic hyperglycaemia in the perioperative setting also seems to be harmful, affecting the rate of postoperative infections and neurological outcomes.^{55,56} A meta-analysis⁵⁷ of 34 trials showed that perioperative insulin infusion reduces mortality but increases rates of hypoglycaemia. However, researchers calculated that the available mortality data were too few to reliably detect a plausible treatment effect, and that the presence of diabetes did not affect outcomes. Thus, hyperglycaemia in patients with or without diabetes could adversely affect outcomes after surgery.

Stress hyperglycaemia is linked to poor outcomes and the association seems to be stronger for patients without diabetes than for those with pre-existing diabetes. However, studies were not prospectively designed to compare patients with stress hyperglycaemia and pre-existing diabetes, creating some limitations. Despite data from interventional studies^{1,2} and controlling for severity of illness, residual confounding could be difficult to completely eliminate. For example, patients with pre-existing diabetes might be more likely to undergo glycaemic monitoring and receive insulin treatment²⁵ or other life-saving drugs⁵⁸ in the hospital than would undiagnosed patients. Additionally, studies lack a consistent or strict definition of stress hyperglycaemia.^{47,51}

Many studies do not have sufficient comparator groups because they are observational. For example, direct comparisons of glycaemic control in non-diabetic patients who have stress hyperglycaemia with diabetic patients are often unable to account for the change in glucose from baseline in the latter. Non-diabetic patients with stress hyperglycaemia should ideally be compared with those who have been diagnosed and who have deterioration of pre-illness glycaemic control to enable assessment of whether outcomes differ. However, results of a few studies^{27,40,49} show poor outcomes that persist in patients with newly discovered hyperglycaemia, after accounting for glycaemic control. Despite these limitations, results of controlled studies seem to show that treatment of hyperglycaemia in patients improves outcomes, although new data indicate that the quest for strict normoglycaemia is harmful.

Pathophysiology

In the hospital setting, a combination of factors affect the development of stress hyperglycaemia (figure 2). The mechanisms for this disorder probably vary with the patients' underlying glucose tolerance, type and severity of disease, and stage of illness. The cause of hyperglycaemia in type 2 diabetes is a combination of insulin resistance and β -cell secretory defects. However, the development of stress hyperglycaemia is caused by a highly complex interplay of counter-regulatory hormones such as catecholamines, growth hormone, cortisol, and cytokines (figure 3).^{34,59,60} The underlying illness might affect the scale of cytokine production and hormonal derangements. Complex feedforward and feedback mechanisms between hormones and cytokines exist,⁶¹ and this neurohormonal environment ultimately leads to excessive hepatic glucose production and insulin resistance.^{59,60} High hepatic output of glucose, especially through gluconeogenesis, seems to be the most important contributor to stress hyperglycaemia.^{62,63} Excessive glucagon is the primary mediator of gluconeogenesis,⁶⁴ although epinephrine⁶⁵ and cortisol⁶⁶ also contribute. Tumour necrosis factor- α (TNF α) might promote gluconeogenesis by stimulating glucagon production.⁶⁷

Insulin resistance during illness is characterised by an inability to suppress central hepatic glucose production. In the periphery, insulin resistance is mediated through two major pathways. Reduced insulin-mediated glucose uptake results from defects in postreceptor insulin signalling⁶⁸ and downregulation of glucose transporter (GLUT)-4.⁶⁹ Additionally, impaired non-oxidative glucose disposal probably results from reduced skeletal muscle glycogen synthesis.⁷⁰ Both excess cortisol⁷¹ and epinephrine⁷² reduce insulin-mediated glucose uptake. Cytokines such as TNF α ,⁷³ and interleukin 1⁷⁴ inhibit postreceptor insulin signalling. Severity of illness is associated with a proportional rise in serum cytokines²⁵ and insulin resistance.⁷⁵ Furthermore, hyperglycaemia exacerbates the cytokine, inflammatory, and oxidative stress response, potentially setting up a vicious cycle whereby hyperglycaemia leads to further hyperglycaemia.^{76–78} Resolution of hyperglycaemia is associated with normalisation of the inflammatory response.⁷⁸

Insulin resistance ultimately promotes a catabolic state in which lipolysis takes place. Excessive circulating free fatty acids in turn exacerbate insulin resistance by disrupting end-organ insulin signalling⁷⁹ and glycogen synthase.⁸⁰ This lipotoxicity aggravates the inflammatory state, paralleling the effects of glucotoxicity.⁸¹ Glucotoxicity, lipotoxicity, and inflammation are key components of what might be viewed as an exaggerated global insulin-resistance syndrome associated with acute illness. These components also promote endothelial dysfunction, which has a complex reciprocal cause–effect relation with insulin resistance.⁸² Hyperinsulinaemia might impart additive consequences to that of hyperglycaemia, including exaggerated inflammatory and counter-regulatory hormone responses and impaired fibrinolysis.^{83,84}

Despite reduced insulin-mediated glucose uptake, an early increase in whole-body glucose uptake takes place—mainly as a result of cytokine-mediated up regulation of GLUT-1.^{85–88} GLUT-1 is a ubiquitous glucose transporter that is involved in non-insulin-mediated glucose uptake. Although non-oxidative metabolism (eg, glycogen synthesis) is impaired, oxidative glucose metabolism is upregulated early.⁸⁹ In addition to patient-specific factors, certain therapeutic interventions such as catecholamine infusions, corticosteroids, and enteral and parenteral nutrition can worsen or precipitate hyperglycaemia.²⁵ No studies of mechanisms comparing critically ill patients with diabetes or stress hyperglycaemia are available. Therefore, whether differences in pathophysiology explain differences in outcomes is unclear.

Mechanism of adverse outcomes

The typical chronic complications of diabetes take several years to develop; therefore, the explanation for a rise in harm that is related to stress hyperglycaemia needs further consideration (figure 4). Stress hyperglycaemia is mediated by much greater inflammatory and neuroendocrine derangements than are expected in chronic hyperglycaemia associated with diabetes. Possibly, these derangements heighten susceptibility to benefits of interventions. For example, multiorgan failure is associated with widespread microvascular endothelial dysfunction, and improved outcomes associated with intensive insulin therapy have been attributed in part to endothelial protection.⁹⁰

Some evidence suggests that chronic hyperglycaemia sets up a pattern of cellular conditioning that might actually be protective of acute hyperglycaemia-mediated damage during critical illness. One mechanism for this effect might be the preferential downregulation of glucose transporters under conditions of chronic rather than intermittent hyperglycaemia. GLUT-1 and GLUT-3 are facilitative glucose transporters that allow glucose to enter cells independently of insulin. Several factors that upregulate these transporters are elaborated during critical illness, potentially allowing glucose to enter cells unchecked by normal downregulatory responses.⁹¹ Thus, a wide range of tissues might be susceptible to enhanced glucose toxicity as a result of acute illness.^{91,92} Whether patients with chronic hyperglycaemia are able to compensate by downregulating glucose transporters is unknown. Various oxidative stressors prevent the downregulation of GLUT-1 transporters in vascular endothelial cells.⁹³

Acute fluctuations in glucose concentrations are associated with mortality in acutely ill patients, independently of mean glucose concentration.^{94–97} Repetitive acute glucose fluctuations induce more endothelial apoptosis,⁹⁸ and greater endothelial dysfunction and oxidative stress responses compared with the less variable excursions both in vitro^{98,99} and in patients with or without known diabetes.^{100,101} Furthermore, oxidative stress seems to have a unifying causal role in the stimulation of classic intracellular pathways that mediate chronic complications of hyperglycaemia.¹⁰² Therefore, increased oxidative stress during acute hyperglycaemia (by contrast with chronic hyperglycaemia or diabetes) would seem to be a plausible mechanism for additive adverse effects of stress hyperglycaemia.

Pre-existing microvascular and macrovascular disease in patients with diabetes might affect outcomes associated with strict glycaemic control. For example, patients with diabetic autonomic dysfunction might be predisposed to development of severe hypoglycaemia as a result of hypoglycaemia unawareness. Patients with cardiac autonomic dysfunction might be predisposed to development of arrhythmias as a result of hypoglycaemia. Furthermore, the response to hypoglycaemia could be more severe in patients with previous evidence of diabetes who have pre-existing endothelial dysfunction and greater tendency for ischaemic events than in those without diabetes.¹⁰³ Hypoglycaemia elicits a counter-regulatory hormonal response that might aggravate the inflammatory state already present in acute illness. Whether hypoglycaemia is an independent indicator of overall risk of death, or merely a marker of severity of illness is unclear.^{104,105} In patients with severe brain injury, changes in glucose transport might in part account for an association of tight glycaemic control with abnormal cerebral glucose metabolism and poor outcomes.¹⁰⁶ Conversely, in the Leuven studies,²¹ a low propensity for hypoglycaemia does not by itself explain any susceptibility to benefits of glucoregulation.

Management

Current guidelines^{107,108} do not recognise stress hyperglycaemia as being different from pre-existing diabetes, although such guidelines might specify separate targets for ICU and

non-ICU patients. Other than the distinction between surgical and medical ICU patients, insufficient data are available to recommend risk stratification for assignment of glucose targets with respect to the cause or severity of hyperglycaemia. However, some investigators have noted that the concept of separate targets is similar to other situations, in which rapid correction of longstanding physiology is detrimental.²² Guidelines are being revised in response to the NICE-SUGAR results. We emphasise that providers “should not abandon glucose management in the ICU setting, but that a less intensive target similar to that of the conventional treatment arm (mean glucose 8 mmol/L) be implemented”.^{109,110} Outside of the ICU, no inpatient data exist to guide treatment decisions, but individualised glucose targets based on outpatient recommendations are reasonable.^{107,108}

No studies have specifically investigated the best method for the management of stress hyperglycaemia. Therefore, to follow general recommendations for hospital inpatients with hyperglycaemia is reasonable, keeping in mind that stress hyperglycaemia by definition is a transient, often dynamic disorder that responds to changes in disease course. Specific recommendations for implementation of glycaemic control generally include insulin therapy, and in the surgical and medical ICU insulin infusions are favoured. Stress hyperglycaemia lends itself ideally to insulin, which is rapidly titratable in response to changes in glucose concentrations. Intravenous insulin is highly effective and can be adjusted frequently. In patients with oedema or hypoperfusion, subcutaneous insulin might result in insulin stacking and hypoglycaemia.¹¹¹ However, intravenous insulin is still relegated to the ICU in many institutions because of concerns about safety and about adequate staffing.

Subcutaneous insulin is reasonable for most general surgical and medical patients outside the ICU. In the outpatient setting, insulin analogues usually produce a lower incidence of hypoglycaemia than do regular human insulin or neutral protamine hagedom (NPH) insulin, but this finding was not confirmed in an inpatient study of patients with type 2 diabetes.¹¹² Results of another randomised controlled trial¹¹³ of insulin naive patients with diabetes showed that subcutaneous basal bolus insulin was better than was sliding-scale insulin for attainment of safe, effective glycaemic control. Investigators were able to safely escalate the dose of insulin daily, but seemed to need up to 3 days to reach a target glucose of 7.8 mmol/L. In another study¹¹⁴ patients who initially received intravenous insulin in the ICU and then were rapidly transitioned to subcutaneous insulin for transfer to the wards had good outcomes.

Carers should take steps to pre-emptively adjust therapy in response to changes in nutritional needs. This strategy could include consistent carbohydrate diets or giving prandial insulin according to estimated carbohydrate intake. During enteral feeding, anticipatory orders, including increased monitoring, withholding insulin, and, if needed, dextrose infusion in case of planned or unplanned interruption are necessary. The amount of exogenous, intravenous, and enteral glucose given is commonly overlooked, and can be restricted when necessary—eg, by changing enteral formulas. No prospective data show that interventions designed specifically to reduce glucose fluctuations improve outcomes. However, fluctuations in glucose might be kept to a minimum with physiological insulin replacement,^{115,116} especially to ensure adequate carbohydrate coverage. Insulin-drip protocols effectively provide basal and correction insulin coverage, but additional subcutaneous short-acting insulin is usually necessary to prevent rapid glucose swings in patients with intermittent exogenous carbohydrate exposure.¹¹⁷ Furthermore, proper training and use of improved algorithms for intravenous insulin could be useful.^{117–120}

Anticipatory reduction in total daily insulin doses of at least 10–20% are sometimes necessary in patients with tight glucose control who are clinically improving. Experts do not advocate the use of oral hypoglycaemic agents for most hospital inpatients because of

the often slow onset and resolution of action, risk of hypoglycaemia in patients with unpredictable nutritional intake, and because of contraindications, such as frequent administration of contrast dye in patients taking metformin.¹⁰⁴

Prevention and monitoring

In most patients, hospital-related hyperglycaemia is not generally predictable or preventable. However, early recognition and interception might prevent its persistence and exacerbation. In patients with diabetes, observational data suggest that long-term preadmission glycaemic control might affect the operative risk for both cardiovascular and non-cardiac complications.^{55,121} Furthermore, preoperative glucotoxicity could affect the ease with which postoperative control is achieved. Although gross intraoperative hyperglycaemia might be deleterious for certain procedures, intraoperative use of strict glycaemic control is still controversial.^{56,57}

The effectiveness and safety of any glycaemic intervention depends upon the ability to accurately monitor glucose. Especially in the ICU, many confounding factors in glucose measurement such as anaemia or hypotension might be present simultaneously, and could render typical bedside capillary point of care devices inaccurate.¹²² Because of their increased severity of illness, glucose measurement in patients with stress hyperglycaemia can be especially challenging. Real-time continuous glucose monitoring with interstitial glucose measurements could potentially reduce the frequency of blood glucose sampling, but this method is even more vulnerable to error and is only approved for adjunctive use.¹²³ Finally, an oral-glucose-tolerance-test or close monitoring at follow-up are needed at discharge to identify patients with underlying diabetes and prevent subacute (eg, infectious) or long-term complications.

Future direction and conclusion

Prospective studies with follow-up data comparing diabetes and stress hyperglycaemia are needed. HbA_{1c} should be reported both to exclude undiagnosed probable diabetes and to infer whether patients with diabetes have stress-related exacerbation of hyperglycaemia. Patients with non-diabetic stress hyperglycaemia should be compared with a subgroup of patients with diabetes who have stress-related exacerbation of hyperglycaemia, and those with non-diabetic normoglycaemia should be compared with those with diabetes whose glucose control was unaltered at admission. Additionally, researchers examining risks and outcomes of hyperglycaemia should place special emphasis on high-risk cardiac subgroups. The optimum target glucose range in stress conditions is still undefined, and different targets should be compared on the basis of their risk-to-benefit ratios.

Until such data are available, efforts to improve ease of use and safety of intensive glycaemic control, such as computerised insulin dosing algorithms and glucose monitoring techniques, might mitigate the need for risk stratification. Stress hyperglycaemia is a heterogeneous entity with unique pathophysiological features. Present practice is to treat hyperglycaemia irrespective of its cause. However, we suggest that the chronicity of hyperglycaemia and other factors specific to patients or populations merits special consideration.

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Search strategy and selection criteria

We searched PubMed with the terms “stress hyperglycemia”, “diabetes”, “hyperglycemia” in conjunction with the key modifying terms “admission”, “hospital”, “inpatient”, “intensive care unit”, “critical care”, “acute myocardial infarction”, and “acute stroke”. We also searched the reference lists of reports identified with this strategy for relevant publications. We prioritised controlled trials or meta-analyses and observational studies from the past 5 years. We used only studies in peer-reviewed journals, focusing on comparisons between stress hyperglycaemia and diabetes.

Panel: Classification of hyperglycaemia in hospital⁹**Known diabetes**

Diabetes diagnosed and treated before admission

Newly diagnosed diabetes

Fasting glucose more than 6.9 mmol/L or random glucose higher than 11.1 mmol/L during hospital stay and confirmed after discharge

Hospital-related hyperglycaemia

Fasting glucose more than 6.9 mmol/L or random glucose higher than 11.1 mmol/L during hospital stay that reverts to normal range after discharge

Figure 1.
Expanded view of stress hyperglycaemia

Figure 2. Multifactorial causes of hospital-related hyperglycaemia

Causal factors are specific to the patient, their illness, and their treatment. Hyperglycaemia can exacerbate some illness-specific factors and increase need for treatment-specific factors, leading to a vicious cycle by which hyperglycaemia causes further hyperglycaemia. HPA=hypothalamic-pituitary-adrenal axis.

Figure 3. Glucose metabolism in stress hyperglycaemia

Stress hyperglycaemia is characterised by increased whole-body glucose uptake, mostly caused by non-insulin-mediated glucose transport via GLUT-1 transporters to body tissues. Insulin-mediated glucose uptake is reduced (insulin resistance), largely due to postreceptor insulin signalling defects that result in reduced GLUT-4-mediated glucose transport in insulin sensitive tissues such as liver, muscle, and fat. Muscle glycogen storage is also reduced. Glucose production is generally up-regulated, mainly a result of unregulated hepatic gluconeogenesis. Finally, once inside a target cell, glucose is oxidised readily but non-oxidative metabolism (predominantly glycogen storage) is impaired.

Figure 4. Overlapping mechanisms of harm in hyperglycaemia

Mechanisms of harm relate to acute or chronic complications of hyperglycaemia. NFκB = nuclear factor κ B.

ERK = extracellular signal regulated kinase. MAPK=microtubule associated protein kinase.

PKC = protein kinase C.

AGE = advanced glycosylation endproducts. CVA = cerebrovascular accident. AMI = acute myocardial infarction.

Table 1

Prevalence of diabetes and impaired glucose tolerance

	Number of patients	Condition	Method of diagnosis	Time of testing	IGT	DM
Wallander et al (2008) ¹¹	122	AMI, AG <11.1 mmol/L	OGTT	Discharge, 3 months, 12 months	31%, 42%, 33%	34%, 27%, 35%
Ishihara et al (2006) ¹²	200	AMI	OGTT	1 week after admission	39%	27%
Hashimoto et al (2005) ¹³	134	ACS, FBG <7 mmol/L or HbA _{1c} <6%	OGTT	Discharge	37%	10%
Bartnik et al (2004) ¹⁴	932	ACS	OGTT	Within 2 months	36%	22%
Gray et al (2004) ¹⁵	62	Stroke+AG 6.1–17 mmol/L	OGTT	3 months	37%	21%
Vancheri et al (2005) ¹⁶	96	Stroke	OGTT	Discharge, 3 months	38.5%, 27.1%	45.8%, 37.5%
Greci et al (2003) ¹⁷	35	Unselected, AG >6.9 mmol/L	Two FBG >6.9 mmol/L or OGTT	When stable as outpatient	..	60%

Prevalence in selected and non-selected populations from patients in hospital. IGT=impaired glucose tolerance. DM=diabetes mellitus. AMI=acute myocardial infarction. AG=admission glucose. OGTT=oral glucose tolerance test (standard 75 g). FBG=fasting blood glucose. ACS=acute coronary syndrome. ..=not available. HbA_{1c}=glycosylated haemoglobin.