Post-ICU Diabetes

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Learning Objectives

This chapter summarises the pathophysiology of stress hyperglycaemia during critical illness, updates evidence that patients post critical illness frequently develop diabetes, outlines putative mechanisms underlying this 'post-intensive care unit (ICU) diabetes' and discusses the potential roles for screening and treatment to prevent post-ICU diabetes and its complications.

10.1 Introduction

Stress hyperglycaemia describes the phenomenon of hyperglycaemia that occurs in critically ill patients in whom glucose tolerance was previously normal and initially resolves following recovery [1]. For this reason, stress hyperglycaemia traditionally has not been considered to have an adverse impact on long-term health [1]. However, it has been recently recognised that there are strong associations between stress hyperglycaemia during intensive care unit (ICU) admission and the subsequent development of type 2 diabetes in ICU survivors [2]. This phenomenon could therefore be referred to as 'post-ICU diabetes'.

An increased risk of diabetes in this group may be of particular importance as survivors of ICU frequently experience long-term complications such as sensorimotor peripheral neuropathy, autonomic neuropathy and nephropathy [3–6], all of which have the potential to be exacerbated by the development of concomitant diabetes. Screening for diabetes is relatively inexpensive and can be performed in numerous health-care settings. Thus, an opportunity may exist for screening and follow-up of patients with stress hyperglycaemia to reduce progression to diabetes and prevent complications associated with long-term hyperglycaemia.

10.2 Stress Hyperglycaemia

'Stress hyperglycaemia' is defined as a blood glucose that, in health, would lead to a diagnosis of diabetes but initially resolves with resolution of the critical illness [7, 8]. It is accepted that stress hyperglycaemia occurs frequently – up to 50% of critically ill patients are hyperglycaemic within 48 hours of ICU admission [8]. The prevalence of stress hyperglycaemia depends upon the glucose threshold used, the population studied and whether patients who have unrecognised type 2 diabetes are excluded from estimates [8]. Studies to identify patients with unrecognised diabetes on hospital admission using glycated haemoglobin (HbA_{1c}) measurements reveal up to 15% of patients have unrecognised diabetes [9]. Nevertheless, even when patients with previously unrecognised diabetes are excluded from estimates, stress hyperglycaemia occurs frequently during critical illness [8].

The pathophysiology of stress hyperglycaemia involves a complex interplay between patient predisposition, the physiological changes associated with critical illness and specific treatments administered in the ICU (Table 10.1). The initial mechanistic studies of stress hyperglycaemia were conducted in war zones. These included blood sampling in soldiers with major injuries and hypovolaemic shock, which identified that the rise in serum insulin in response to the hyperglycaemia was inadequate, particularly as injury severity increased [10]. Insulin secretion was thought to be attenuated due to effects of counter-regulatory hormones on islet cells [10].

Table 10.1 Causes of stress hyperglycaemia in critical illness

Individual patient predisposition	ICU treatments	Physiological changes due to critical illness
Insulin resistance Pancreatic β-cell reserve	Total parenteral nutrition Enteral nutrition Vasopressors Glucocorticoids Dextrose	Increased counter-regulatory hormones (glucagon, cortisol, catecholamines) Inflammatory cytokines (TNF-α, IL-1, IL-6) alter insulin receptor signalling Increased lipolysis: circulating free fatty acids alter insulin receptor signalling

Patient predisposition, physiological changes during critical illness and treatments administered in the ICU can all contribute to the development of stress hyperglycaemia
ICU intensive care unit, *TNF* tumour necrosis factor, *IL* interleukin

It is now considered that the pathogenesis of stress hyperglycaemia is predominately a state of insulin resistance coupled with relative insulin deficiency (insufficient plasma insulin levels to meet demand) [1]. The stress response to critical illness initiates significant activation of inflammatory mediators and a rise in counter-regulatory hormones, both of which increase hepatic gluconeogenesis and drive insulin resistance. Insulin resistance results largely from post-receptor insulin signalling defects in glucose transporters type 4 (GLUT-4) leading to reduced glucose uptake in insulin-sensitive tissues (liver, muscle and fat) [11]. Muscle glycogen storage is also impaired in stress hyperglycaemia [1].

Whether stress hyperglycaemia *per se* is harmful or an epiphenomenon of illness severity is uncertain. During critical illness, stress hyperglycaemia is a known marker of illness severity and the degree of hyperglycaemia is strongly associated with mortality, especially in patients without a history of diabetes [8, 12]. However, there is no conclusive evidence proving this is a causative association. Whilst there is likely to be some concentration at which hyperglycaemia will be harmful, 'mild' stress hyperglycaemia may represent an epiphenomenon [13] or even an adaptive physiological response to critical illness that augments cellular glucose uptake in non-insulin-dependent tissues (such as the nervous system, bone marrow and the reticuloendothelial system), in the setting of the diminished microvascular flow frequently associated with critical illness [14]. The latter hypothesis is supported by the NICE-SUGAR trial. Within this landmark multi-centre trial, tight control of stress hyperglycaemia with intensive insulin therapy (4.4–6.1 mmol/L) when compared to standard care (6–10 mmol/L) increased mortality [15].

10.3 Stress Hyperglycaemia, Prediabetes and Type 2 Diabetes: A Continuum?

It is biologically plausible that critical illness also unmasks latent insulin resistance and/or impaired pancreatic β-cell secretory function in a proportion of susceptible patients [16]. Accordingly, stress hyperglycaemia may identify a cohort at greater risk of subsequent diabetes, even years after survival from critical illness.

Transient hyperglycaemia which occurs in other contexts of physiological 'stress' (i.e. not critical illness) can predict the subsequent development of type 2 diabetes. For example, whilst gestational diabetes was once considered to be a temporary disorder of

pregnancy, it is now well recognised that gestational diabetes strongly predicts the development of type 2 diabetes [17–19]. Screening programmes have been widely implemented postpartum for women with gestational diabetes in order to identify prediabetes and type 2 diabetes early and thereby reduce complications [20, 21].

Furthermore, a number of epidemiological studies have reported an association between hyperglycaemia during hospitalisation that does not involve admission to ICU and the subsequent development of type 2 diabetes (Table 10.2) [22–25]. The most externally valid of these studies to the critical care environment was a retrospective data-linkage study of 86,634 patients admitted to hospital from emergency departments in Scotland [22]. The 3-year risk of developing diabetes for patients who were hyperglycaemic (blood glucose >11 mmol/L) was 10% compared to 2.3% for all patients requiring emergency admission [22].

The mechanisms which underlie progressive glucose intolerance and the development of prediabetes or post-ICU diabetes are likely to be complex and have been infrequently studied (Fig. 10.1). It is plausible that stress hyperglycaemia during ICU identifies those patients with pre-existing impaired β-cell reserve and insulin resistance, but it is possible that critical illness itself accelerates these abnormalities. If insulin resistance persists following critical illness, it is likely to contribute to the development of post-ICU diabetes [26]. The hyperglycaemia which occurs in type 2 diabetes typically results from progressive insulin resistance which develops over years and contributes to ensuing beta-cell secretory defect [27]. However, the insulin resistance of critical illness occurs rapidly, as a result of a dramatic rise in counter-regulatory hormones and inflammatory mediators [1]. Whether insulin resistance persists following critical illness in patients who experienced stress hyperglycaemia and the magnitude of any such persisting insulin resistance have never been evaluated.

In addition to persisting insulin resistance, a number of other mechanisms may be implicated. In health, the gastrointestinal tract plays a key role in the modulation of postprandial glycaemic excursions, with postprandial glycaemia dependent largely on both the rate of gastric emptying and the incretin enterohormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) [28]. Loss of postprandial glycaemic control is frequently the first sign of disordered glycaemic control in those that develop type 2 diabetes [29], and postprandial hyperglycaemia has the capacity to contribute to the development of diabetes via glucose toxicity to pancreatic β-cells [27]. The 'incretin effect' describes the increased insulin release following enteral glucose administration when compared with iso-glycaemic intravenous glucose administration [28]. GLP-1 and GIP, which are secreted by the intestine in response to food ingestion, are responsible for the incretin effect and account for up to 70% of the total insulin response to oral glucose in health [30]. There is emerging evidence that the incretin effect is acutely diminished during critical illness, although whether this simply represents attenuated secretion of GIP and GLP-1 or more complex pathophysiology, such as reduced insulinotropic effects of GIP and GLP-1 in the critically ill, remains unknown [31–34]. It should be recognised that measurement of the incretin effect after intragastric administration of nutrient in the critically ill is biased toward a diminished incretin effect: this is because secretion of GIP and GLP-1 are dependent on the rate of gastric emptying [35], and gastric emptying is frequently delayed during critical illness [36]. It is unclear whether attenuation of the incretin effect persists after resolution of critical illness.

The role of gastric dysmotility in the development of post-ICU diabetes has also never been studied. Gastric dysmotility occurs frequently during critical illness [36, 37], but limited data exist about gastric emptying as patients recover [6]. Rapid gastric emptying can lead to larger postprandial glycaemic excursions and may be implicated in the

Table 10.2 Conditions in which stress hyperglycaemia has been found to predict incident diabetes in adult patients outside the ICU setting

Condition	Study design and location	Cohort size	SH definition	Method used to diagnose incident diabetes	Duration of follow-up	Risk of incident diabetes
Hospital admission via emergency department [22]	Multi-centre, RC, Scotland	86,634	Admission BG ≥11.1 mmol/L	Record in national diabetes register (>99% capture rate)	3 years	Incidence in SH: 9.9% (95% CI 9.2–10.6) vs control: <1%
Gestational diabetes [17–19]	Typically multi-centre, either RC or PC studies	Up to 659,164 per study	Various consensus criteria	Annual OGTT	Up to 20 years	Relative risk 7.43 (95% CI 4.79–11.51) from meta-analysis
Myocardial infarction [23]	Multi-centre, RC, United States	10,499	Admission BG ≥7.8 mmol/L	Diagnostic codes, medication prescriptions and/or HbA_{1c} ≥6.5%	6 months	Incidence in SH: 11.8% vs control: 5.1%; odds ratio 2.56 (95% CI 2.15–3.06)
Pneumonia requiring hospitalisation [24]	Multi-centre, PC, Canada	3145	Admission BG ≥11.1 mmol/L	Physician insurance claims and/or hospital diagnostic codes	5 years	Incidence in SH: 47% vs control: 6%; adjusted hazard ratio 11.43 (95% CI 7.50–17.42)
Stroke [25]	Single centre, PC, England	62	Admission BG 6.1–17 mmol/L and no history of diabetes	OGTT	3 months	Incidence 21%, no control group

The methods used to exclude baseline unrecognised diabetes differed among studies
SH stress hyperglycaemia, *RC* retrospective cohort, *BG* blood glucose, *CI* confidence interval, *PC* prospective cohort, *OGTT* oral glucose tolerance test, *HbA_{1c}* glycated haemoglobin

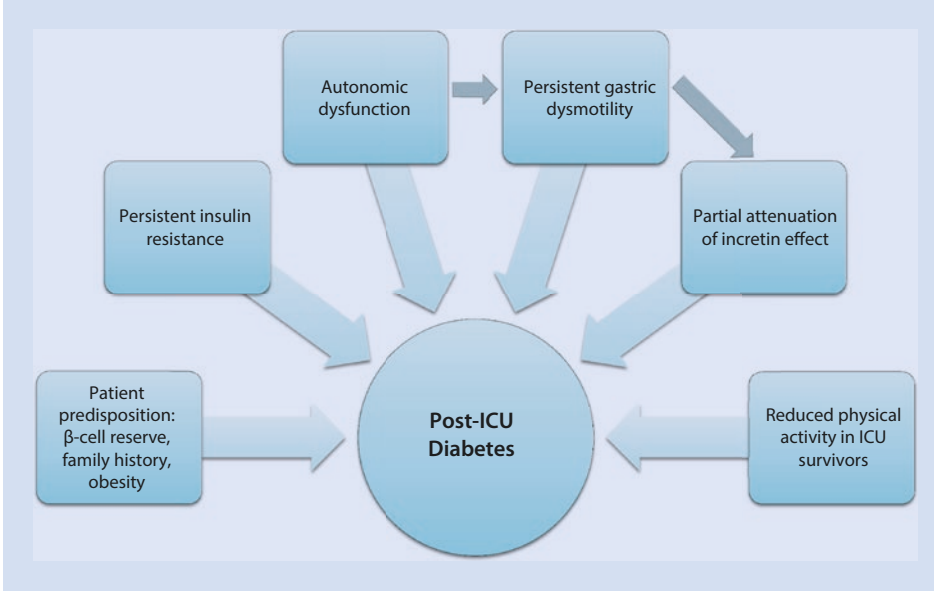

Fig. 10.1 Summary of postulated mechanisms contributing to the development of post-ICU diabetes. A combination of predisposing factors in the patient and physiological changes associated with critical illness may be implicated

pathogenesis of type 2 diabetes [38–40], but delayed gastric emptying can also potentially contribute to hyperglycaemia via a reduction in the incretin effect [41]. Therefore, persistent gastric dysmotility has the potential to contribute to persistent glucose intolerance following critical illness.

Additional mechanisms that may predispose to post-ICU diabetes and warrant further evaluation include the reduction in physical activity and autonomic dysfunction, both of which are reported to occur frequently in survivors of ICU [42, 43]. Physical inactivity and autonomic dysfunction have the capacity to worsen glycaemia and facilitate the earlier development of microvascular complications associated with diabetes [44, 45]. Finally, critically ill patients who experience stress hyperglycaemia are reported to more frequently have a family history of diabetes and a higher body mass index on admission to ICU than critically ill patients with normal glucose tolerance [46, 47]. This suggests that well-accepted risk factors of type 2 diabetes, such as obesity and family history, may also play a key role in the development of post-ICU diabetes.

10.4 Evidence that Stress Hyperglycaemia Predicts Type 2 Diabetes After Critical Illness

The question of whether stress hyperglycaemia identifies survivors of critical illness at increased risk of subsequently developing diabetes has been the subject of a number of retrospective and prospective controlled cohort studies [22, 46–49] and a meta-analysis [2]. The original studies used different methods to determine the risk of incident diabetes and employed various definitions of stress hyperglycaemia (Table 10.3). Two of the prospective cohort studies were conducted in a single centre in Croatia and tested patients

Table 10.3 Summary of studies examining the risk of incident prediabetes and diabetes in survivors of critical illness who experienced stress hyperglycaemia

Study design and location	Participants	SH definition	Method used to (a) diagnose incident diabetes and (b) exclude baseline diabetes	Number of patients completing follow-up	Risk of incident prediabetes	Risk of incident diabetes
Single-centre, PC, Croatia [46]	1029 medical ICU patients with no history of steroid use, pancreatitis, disturbed glucose metabolism or other endocrine disorder	Venous BG in ICU >7.7 mmol/L measured twice per day with point-of-care blood gas analyser	(a) Annual OGTT for 5 years[a] (b) History; OGTT 4–6 weeks after discharge	591	Relative risk 2.3 (95% CI 1.6–3.4)	Relative risk 5.6 (95% CI 3.1–10.2)
Single-centre, PC, Croatia [48]	258 patients admitted to ICU with sepsis, acute coronary syndrome and acute heart failure with no history of disturbed glucose metabolism or steroid use	Random venous BG in ICU >7.7 mmol/L on at least two occasions	(a) Annual OGTT for 5 years but frequency not specified[a] (b) History; absence of hyperglycaemia before discharge	166	Relative risk 1.97 (95% CI 1.04–3.73)	Relative risk 4.51 (95% CI 1.42–14.30)
Single-centre, PC, Belgium [47]	385 patients aged 18–85 years admitted to a medical-surgical ICU for ≥48 h; patients with pancreatitis, known disturbed glucose metabolism and those using glucose-lowering drugs excluded	Arterial BG >140 mg/dL (>7.8 mmol/L) measured using on-site blood gas analyser	(a) OGTT with or without HbA_{1c} 8 months after ICU admission[a] (b) History; medication review; with or without HbA_{1c}	338	Odds ratio 1.43 (95% CI 0.82–2.50)	Odds ratio 1.95 (95% CI 0.65–5.86)

(continued)

Table 10.3 (continued)

Study design and location	Participants	SH definition	Method used to (a) diagnose incident diabetes and (b) exclude baseline diabetes	Number of patients completing follow-up	Risk of incident prediabetes	Risk of incident diabetes
Multi-centre, RC, Australia [49]	22,473 adult patients surviving ICU admission in Australia; 17,074 without known diabetes	Peak BG within first 24 hours of ICU admission ≥11.1 mmol/L as recorded in national ICU database	(a) Registration with national diabetes register from 30 days up to 8 years after hospital discharge (capture rate 80%); median follow-up 5.3 years (b) Prior record in national diabetes register or record within 30 days of discharge; ICD-10 hospital codes; or peak BG >20 mmol/L	22,473	Not evaluated	Hazard ratio 1.91 (95% CI 1.62–2.26)

SH stress hyperglycaemia, *PC* prospective cohort, *ICU* intensive care unit, *BG* blood glucose, *OGTT* oral glucose tolerance test, *CI* confidence interval, *HbA_{1c}* glycated haemoglobin, *ICD* International Classification of Diseases

[a]Diabetes was defined according to American Diabetes Association criteria [50]: diabetes – fasting plasma glucose ≥7.0 mmol/L or 2-hour plasma glucose during 75 g OGTT ≥11.1 mmol/L or HbA_{1c} ≥6.5% (48 mmol/mol)

after ICU discharge for prediabetes and diabetes [46, 48]. In the study with the most rigorous follow-up, 582 patients underwent annual oral glucose tolerance tests for 5 years after discharge from the ICU [46]. Patients who experienced stress hyperglycaemia during ICU admission (defined as peak blood glucose >7.7 mmol/L) had a fivefold increased risk of developing diabetes when compared to patients without stress hyperglycaemia. In another study from the same centre, 258 patients admitted to ICU with sepsis, acute coronary syndrome or acute heart failure were also followed up with oral glucose tolerance testing [48]. The risk of incident diabetes was more than four times higher in the stress hyperglycaemia cohort. Whilst the results of these studies are informative, generalisability is limited because of the single-centre study design and the absence of reported illness severity data. In contrast, stress hyperglycaemia (peak blood glucose >7.7 mmol/L) did not identify patients at increased risk of incident diabetes in a similar single-centre study of 385 ICU survivors conducted in Belgium [47]. This contrasting finding may be explained by the comparatively short follow-up period – the primary outcome (development of diabetes) was determined using oral glucose tolerance testing, with or without HbA_{1c} testing, at 8 months after ICU discharge.

The retrospective multi-centre database record linkage study of 86,634 patients admitted to hospital from emergency departments in Scotland (summarised in Table 10.2) included a cohort of 1828 patients who required ICU admission and used a higher threshold to define stress hyperglycaemia than other studies (blood glucose ≥11.1 mmol/L) [22]. Data from the cohort of ICU survivors included in this Scottish study was combined with data from the European single-centre prospective cohort studies [46–48] in a recent meta-analysis [2]. A total of 2923 ICU survivors and 131 cases of incident diabetes were included in the meta-analysis. Stress hyperglycaemia was associated with an increased risk of developing diabetes in survivors of critical illness, with a low-moderate degree of statistical heterogeneity between studies (odds ratio 3.48; 95% confidence interval (CI) 2.02–5.98; I^2 = 36.5%) (Fig. 10.2). Stress hyperglycaemia also identified patients at increased risk of developing prediabetes (defined according to the American Diabetes Association criteria [50]), which is a known risk factor for type 2 diabetes, with an annual conversion rate of 5–10% [51]. A limitation of this meta-analysis was the significant clinical heterogeneity among the included studies.

The largest cohort studied to evaluate whether an association between stress hyperglycaemia and subsequent diabetes exists is a multi-centre retrospective data-linkage cohort of 22,473 patients surviving ICU admission in the state of South Australia [49]. Data that was forwarded to the national (Australian New Zealand Intensive Care Society) ICU database were linked to state-retained hospital-level coding data (matching hospital diagnostic codes for diabetes prior to index hospital discharge), registration with the national diabetes register and the national register of deaths. Stress hyperglycaemia (defined as blood glucose ≥11.1 mmol/L in the first 24 hours of admission) occurred in 17% of patients without diabetes, and the incidence of diabetes following critical illness was almost 5% over a median observation period of 5 years. Stress hyperglycaemia nearly doubled the risk of incident diabetes, and this risk persisted regardless of age or illness severity. This study used the proposed cut-off (blood glucose ≥11.1 mmol/L) at which screening programmes may be beneficial [22]. However, like in several of the previous studies [22, 46, 47], only a single elevated reading was required, which may not be sufficiently specific given that temporary disturbances in blood glucose can occur following use of catecholamines or glucocorticoids in critical illness.

In summary, current evidence suggests that the presence of stress hyperglycaemia during critical illness at least doubles the risk of incident diabetes following hospital discharge.

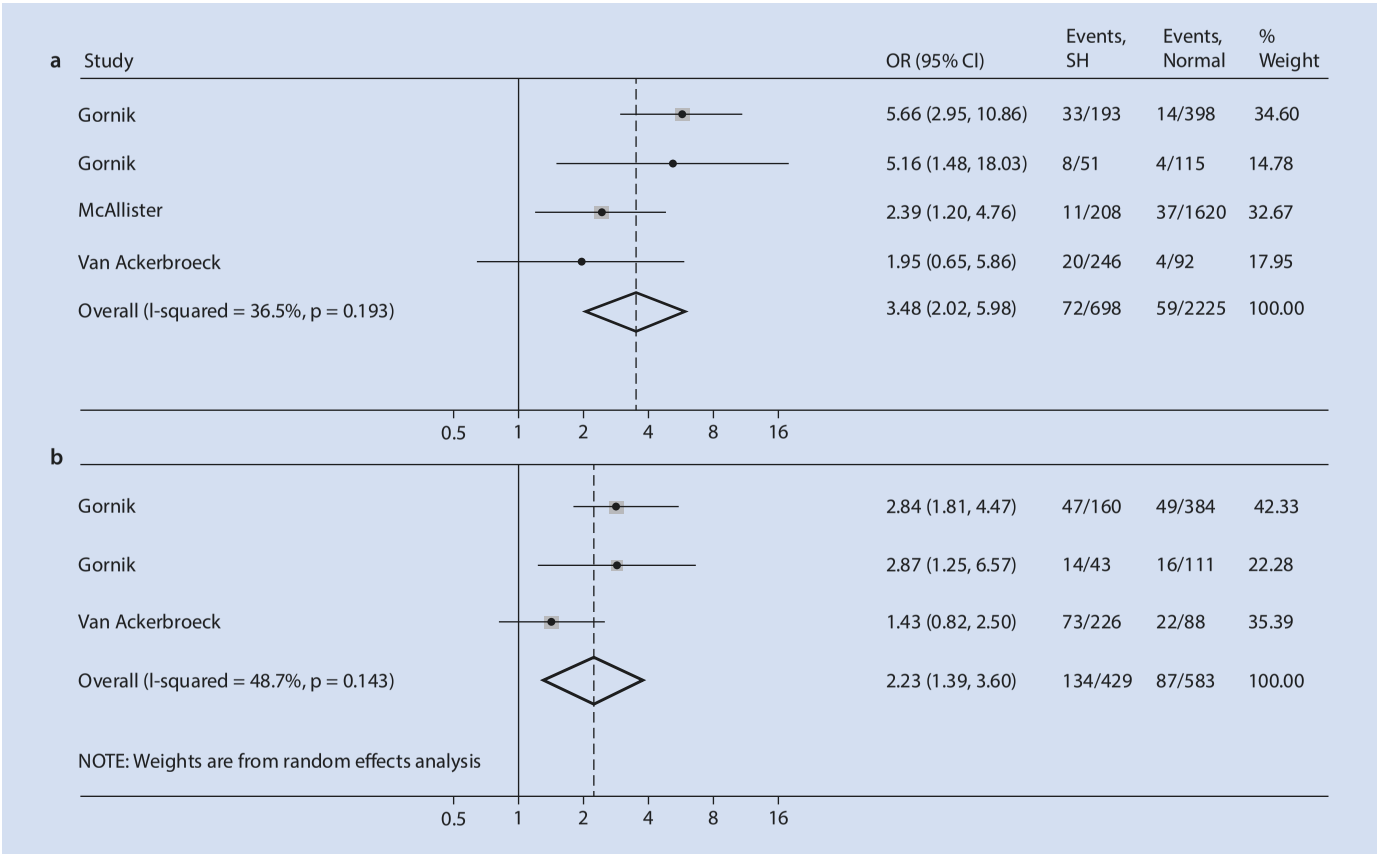

Fig. 10.2 Forest plot showing the risk of **a** incident diabetes and **b** prediabetes in adult ICU patients with stress hyperglycaemia (*Image originally published by BioMed Central* [2]). SH stress hyperglycaemia. Four studies were included in the meta-analysis [22, 46–48]. Prediabetes was defined according to American Diabetes Association criteria [50]: fasting plasma glucose 5.6–6.9 mmol/L (impaired fasting glucose) or 2-hour plasma glucose during 75 g OGTT 7.8–11.0 mmol/L (impaired glucose tolerance) or HbA_{1c} 5.7–6.4% (39–46 mmol/mol)

Accordingly, post-ICU diabetes appears to be a real phenomenon. However, all studies to date have been limited by the use of varying blood glucose thresholds to define stress hyperglycaemia, and blood glucose concentrations have not been reported in relation to nutrient delivery or fasting status. Furthermore, very few studies have measured HbA_{1c} as a way to exclude baseline diabetes, leading to the potential that undiagnosed diabetes may bias estimates of risk.

10.5 Similarities Between the Long-Term Complications of Critical Illness and Those of Diabetes

Many of the complications of critical illness are similar to the known microvascular complications of type 2 diabetes. Nephropathy, autonomic neuropathy and sensorimotor peripheral neuropathy all occur frequently in survivors of critical illness [3–5] and also in patients with type 2 diabetes who have never been critically ill [52]. It is therefore plausible that the development of diabetes after critical illness could exacerbate any underlying long-term complications of critical illness.

Taking nephropathy as an example, critically ill patients who survive an episode of acute kidney injury requiring renal replacement therapy frequently experience poor physical function and mental health even 3 years after hospital discharge [53, 54]. These patients are also at ongoing risk of high mortality and, in those patients still alive at 4 years, albuminuria is present in almost half [55]. Given that albuminuria is a recognised independent risk factor for dialysis requirement, cardiovascular disease and death in cohorts of non-critically ill patients [56, 57] and that albuminuria is a key feature of diabetic nephropathy, it is likely that outcomes will be worse in critically ill patients who subsequently develop diabetes.

Similarly, autonomic dysfunction, which is already prevalent in critical illness and also develops as a complication of type 2 diabetes [58], may be accelerated in at-risk patients and exacerbate symptoms associated with gastroparesis [36] and sexual and bladder dysfunction [59, 60]. Cardiovascular autonomic dysfunction is also strongly associated with mortality both in critically ill cohorts [4] and in patients with type 2 diabetes in the community setting [61] – whether this risk of death is compounded in survivors of critical illness with type 2 diabetes remains unknown.

Finally, the prolonged severe weakness and disability associated with critical illness polyneuropathy [3, 62] may be less likely to recover if post-ICU diabetes develops, given that the known microvascular complications of diabetes include diabetic neuropathy [63, 64].

A significant overlap exists between the long-term complications of critical illness and those of type 2 diabetes, suggesting potential benefits from screening and preventative interventions for prediabetes and type 2 diabetes in survivors at risk of post-ICU diabetes.

10.6 Screening for Post-ICU Diabetes and Potential Preventative Strategies

There is typically an extended time period between the development of type 2 diabetes and its eventual diagnosis, and this delay in clinical diagnosis frequently exacerbates progression of microvascular complications [65]. Therefore, an opportunity exists to explore whether screening programmes in survivors of critical illness who experienced stress

hyperglycaemia can lead to early diagnosis of prediabetes or diabetes and allow intervention to prevent long-term complications. Such a targeted strategy represents a novel approach given that the current evidence base supporting follow-up programmes and interventions for heterogeneous cohorts of ICU survivors is limited [66–69].

It should be recognised that mass general population screening programmes for type 2 diabetes are not always effective [70]. However, targeted screening of groups at high risk, such as women with a history of gestational diabetes, can lead to earlier diagnosis and better health outcomes. In many countries, screening programmes have been instituted during the postpartum period for women with gestational diabetes [20, 71]. Point estimates from meta-analyses suggest that the risk of diabetes following stress hyperglycaemia during critical illness is similar to, or greater than, the risk in women with gestational diabetes over comparable periods of observation [2, 17, 19]. Given the high prevalence of stress hyperglycaemia and that millions of patients are admitted to ICUs worldwide each year, there is potentially a large number of ICU survivors who may benefit from screening and early detection of diabetes or prediabetes. Furthermore, the largest study to date has identified that the risk of incident diabetes following stress hyperglycaemia is greatest in survivors of critical illness aged 50–59 years – a sevenfold increased risk [49]. This is significant because the most cost-effective screening programmes are those which can identify younger populations at risk who have the most potential to benefit from early intervention [72].

The optimal time to screen, duration of screening and best screening test to use (fasting plasma glucose, the 2-hour plasma glucose value during a 75 g oral glucose tolerance test, HbA_{1c} or all of these) for survivors of critical illness are unknown. In critically ill patients with stress hyperglycaemia, HbA_{1c} is reported to be greater than in patients with normal glucose tolerance [47, 73] and, in ambulant populations, HbA_{1c} is a strong predictor of the future risk of diabetes [74]. Repeat HbA_{1c} measurement after ICU discharge to monitor for increments may identify those patients progressing to type 2 diabetes [73] and has the appealing properties of being relatively inexpensive and available at laboratories or primary health-care facilities external to a large hospital that has an ICU, but this has not been studied to date. It is important to note that in other cohorts the benefit of interventions for primary prevention of type 2 diabetes [75, 76] has mainly been demonstrated in patients with impaired glucose tolerance, rather than in individuals with isolated impaired fasting glucose or for those with prediabetes defined by HbA_{1c} criteria. Interventions proven to prevent progression to diabetes in patients diagnosed with prediabetes are however cost-effective and readily available. These interventions include lifestyle modifications such as dietary change, exercise programmes and use of metformin particularly in patients with obesity or prior gestational diabetes [21, 75, 77–80]. None of these interventions have been studied specifically following critical illness.

10.7 Future Directions

There is emerging evidence that stress hyperglycaemia is a risk factor for incident diabetes in survivors of critical illness. To precisely quantify this risk, a multi-centre prospective cohort study with an adequate follow-up period of several years is required. In such a study, it would be important to utilise HbA1c to exclude undiagnosed diabetes at baseline and to define stress hyperglycaemia relative to nutrient delivery and on the basis of repeated blood glucose measurements. In addition, studies which evaluate the mechanisms underlying progressive glucose intolerance following critical illness are needed in

order to guide interventions. Future mechanistic studies could also evaluate autonomic function, insulin and incretin hormone secretion capacity, persistence of insulin resistance (using iso-glycaemic hyperinsulinaemic clamps or sophisticated modelling post oral glucose tolerance testing), persistence of gastric dysmotility, interaction with known risk factors (such as increased body mass index and family history) and physical activity levels post ICU. Finally, it is important to determine whether targeted screening programmes in survivors of critical illness can lead to earlier diagnosis of prediabetes or diabetes and reduce the associated complications that are important to patients.

Conclusion

Stress hyperglycaemia during critical illness is prevalent and appears to identify patients at increased risk of developing diabetes following ICU discharge. The mechanisms underlying post-ICU diabetes remain incompletely understood at present. Further work to determine whether screening and preventative programmes for survivors of critical illness and stress hyperglycaemia are of benefit and cost-effective is required.

Take Home Messages

- Stress hyperglycaemia occurs frequently in the ICU.
- Patients who develop stress hyperglycaemia may be at increased risk of developing type 2 diabetes – current evidence suggests that stress hyperglycaemia may at least double this risk.
- Potential mechanisms implicated in the development of post-ICU diabetes include persistent insulin resistance, autonomic dysfunction, gastric dysmotility, attenuation of the incretin effect, reduced physical activity and individual patient predisposition.
- Post-ICU diabetes can be diagnosed by fasting plasma glucose, an oral glucose tolerance test or HbA1c measurement, using the same diagnostic criteria as type 2 diabetes.
- Patients who experience stress hyperglycaemia during critical illness may benefit from closer follow-up after ICU, but as yet there are no screening programmes or interventions that are proven to be of benefit in this group specifically.

References

1. Dungan KM, Braithwaite SS, Preiser JC. Stress hyperglycaemia. Lancet. 2009;373(9677):1798–807.
2. Ali Abdelhamid Y, Kar P, Finnis ME, Phillips LK, Plummer MP, Shaw JE, et al. Stress hyperglycaemia in critically ill patients and the subsequent risk of diabetes: a systematic review and meta-analysis. Crit Care. 2016;20(1):301.
3. Kress JP, Hall JB. ICU-acquired weakness and recovery from critical illness. N Engl J Med. 2014;370(17):1626–35.
4. Schmidt H, Hoyer D, Hennen R, Heinroth K, Rauchhaus M, Prondzinsky R, et al. Autonomic dysfunction predicts both 1- and 2-month mortality in middle-aged patients with multiple organ dysfunction syndrome. Crit Care Med. 2008;36(3):967–70.
5. Uchino S, Kellum JA, Bellomo R, Doig GS, Morimatsu H, Morgera S, et al. Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA. 2005;294(7):813–8.
6. Nguyen TAN, Ali Abdelhamid Y, Weinel LM, Hatzinikolas S, Kar P, Summers MJ, et al. Postprandial hypotension in older survivors of critical illness. J Crit Care. 2018;45:20–6.
7. Deane AM, Horowitz M. Dysglycaemia in the critically ill – significance and management. Diabetes Obes Metab. 2013;15(9):792–801.

8. Plummer MP, Bellomo R, Cousins CE, Annink CE, Sundararajan K, Reddi BA, et al. Dysglycaemia in the critically ill and the interaction of chronic and acute glycaemia with mortality. Intensive Care Med. 2014;40(7):973–80.
9. Kar P, Jones KL, Horowitz M, Deane AM. Management of critically ill patients with type 2 diabetes: the need for personalised therapy. World J Diabetes. 2015;6(5):693–706.
10. Carey LC, Lowery BD, Cloutier CT. Blood sugar and insulin response of humans in shock. Ann Surg. 1970;172(3):342–50.
11. Plummer MP, Deane AM. Dysglycemia and glucose control during sepsis. Clin Chest Med. 2016;37(2):309–19.
12. Egi M, Bellomo R, Stachowski E, French CJ, Hart GK, Hegarty C, et al. Blood glucose concentration and outcome of critical illness: the impact of diabetes. Crit Care Med. 2008;36(8):2249–55.
13. Kaukonen KM, Bailey M, Egi M, Orford N, Glassford NJ, Marik PE, et al. Stress hyperlactatemia modifies the relationship between stress hyperglycemia and outcome: a retrospective observational study. Crit Care Med. 2014;42(6):1379–85.
14. Marik PE, Bellomo R. Stress hyperglycemia: an essential survival response! Crit Care Med. 2013;41(6):e93–4.
15. Investigators N-SS, Finfer S, Chittock DR, Su SY, Blair D, Foster D, et al. Intensive versus conventional glucose control in critically ill patients. N Engl J Med. 2009;360(13):1283–97.
16. Smith FG, Sheehy AM, Vincent JL, Coursin DB. Critical illness-induced dysglycaemia: diabetes and beyond. Crit Care. 2010;14(6):327.
17. Bellamy L, Casas JP, Hingorani AD, Williams D. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. Lancet. 2009;373(9677):1773–9.
18. Buchanan TA. Pancreatic B-cell defects in gestational diabetes: implications for the pathogenesis and prevention of type 2 diabetes. J Clin Endocrinol Metab. 2001;86(3):989–93.
19. Ben-Haroush A, Yogev Y, Hod M. Epidemiology of gestational diabetes mellitus and its association with type 2 diabetes. Diabet Med. 2004;21(2):103–13.
20. Kim C, Herman WH, Vijan S. Efficacy and cost of postpartum screening strategies for diabetes among women with histories of gestational diabetes mellitus. Diabetes Care. 2007;30(5):1102–6.
21. Aroda VR, Christophi CA, Edelstein SL, Zhang P, Herman WH, Barrett-Connor E, et al. The effect of lifestyle intervention and metformin on preventing or delaying diabetes among women with and without gestational diabetes: the Diabetes Prevention Program outcomes study 10-year follow-up. J Clin Endocrinol Metab. 2015;100(4):1646–53.
22. McAllister DA, Hughes KA, Lone N, Mills NL, Sattar N, McKnight J, et al. Stress hyperglycaemia in hospitalised patients and their 3-year risk of diabetes: a Scottish retrospective cohort study. PLoS Med. 2014;11(8):e1001708.
23. Shore S, Borgerding JA, Gylys-Colwell I, McDermott K, Ho PM, Tillquist MN, et al. Association between hyperglycemia at admission during hospitalization for acute myocardial infarction and subsequent diabetes: insights from the veterans administration cardiac care follow-up clinical study. Diabetes Care. 2014;37(2):409–18.
24. MacIntyre EJ, Majumdar SR, Gamble JM, Minhas-Sandhu JK, Marrie TJ, Eurich DT. Stress hyperglycemia and newly diagnosed diabetes in 2124 patients hospitalized with pneumonia. Am J Med. 2012;125(10):1036 e17–23.
25. Gray CS, Scott JF, French JM, Alberti KG, O'Connell JE. Prevalence and prediction of unrecognised diabetes mellitus and impaired glucose tolerance following acute stroke. Age Ageing. 2004;33(1):71–7.
26. Preiser JC, de Longueville C. Could type 2 diabetes be a component of the post-intensive care syndrome? Crit Care. 2017;21(1):26.
27. Fonseca VA. Defining and characterizing the progression of type 2 diabetes. Diabetes Care. 2009;32(Suppl 2):S151–6.
28. Plummer MP, Chapman MJ, Horowitz M, Deane AM. Incretins and the intensivist: what are they and what does an intensivist need to know about them? Crit Care. 2014;18(2):205.
29. Monnier L, Colette C, Dunseath GJ, Owens DR. The loss of postprandial glycemic control precedes stepwise deterioration of fasting with worsening diabetes. Diabetes Care. 2007;30(2):263–9.
30. Baggio LL, Drucker DJ. Biology of incretins: GLP-1 and GIP. Gastroenterology. 2007;132(6):2131–57.
31. Nielsen ST, Janum S, Krogh-Madsen R, Solomon TP, Moller K. The incretin effect in critically ill patients: a case-control study. Crit Care. 2015;19:402.

32. Deane AM, Rayner CK, Keeshan A, Cvijanovic N, Marino Z, Nguyen NQ, et al. The effects of critical illness on intestinal glucose sensing, transporters, and absorption. Crit Care Med. 2014;42(1):57–65.
33. Kar P, Cousins CE, Annink CE, Jones KL, Chapman MJ, Meier JJ, et al. Effects of glucose-dependent insulinotropic polypeptide on gastric emptying, glycaemia and insulinaemia during critical illness: a prospective, double blind, randomised, crossover study. Crit Care. 2015;19:20.
34. Deane AM, Chapman MJ, Fraser RJ, Burgstad CM, Besanko LK, Horowitz M. The effect of exogenous glucagon-like peptide-1 on the glycaemic response to small intestinal nutrient in the critically ill: a randomised double-blind placebo-controlled cross over study. Crit Care. 2009;13(3):R67.
35. Pilichiewicz AN, Chaikomin R, Brennan IM, Wishart JM, Rayner CK, Jones KL, et al. Load-dependent effects of duodenal glucose on glycemia, gastrointestinal hormones, antropyloroduodenal motility, and energy intake in healthy men. Am J Physiol Endocrinol Metab. 2007;293(3):E743–53.
36. Kar P, Jones KL, Horowitz M, Chapman MJ, Deane AM. Measurement of gastric emptying in the critically ill. Clin Nutr. 2015;34(4):557–64.
37. Gungabissoon U, Hacquoil K, Bains C, Irizarry M, Dukes G, Williamson R, et al. Prevalence, risk factors, clinical consequences, and treatment of enteral feed intolerance during critical illness. JPEN J Parenter Enteral Nutr. 2015;39(4):441–8.
38. Phillips WT, Schwartz JG, McMahan CA. Rapid gastric emptying in patients with early non-insulin-dependent diabetes mellitus. N Engl J Med. 1991;324(2):130–1.
39. Bertin E, Schneider N, Abdelli N, Wampach H, Cadiot G, Loboguerrero A, et al. Gastric emptying is accelerated in obese type 2 diabetic patients without autonomic neuropathy. Diabetes Metab. 2001;27(3):357–64.
40. Phillips LK, Deane AM, Jones KL, Rayner CK, Horowitz M. Gastric emptying and glycaemia in health and diabetes mellitus. Nat Rev Endocrinol. 2015;11(2):112–28.
41. Marathe CS, Rayner CK, Bound M, Checklin H, Standfield S, Wishart J, et al. Small intestinal glucose exposure determines the magnitude of the incretin effect in health and type 2 diabetes. Diabetes. 2014;63(8):2668–75.
42. Herridge MS, Tansey CM, Matte A, Tomlinson G, Diaz-Granados N, Cooper A, et al. Functional disability 5 years after acute respiratory distress syndrome. N Engl J Med. 2011;364(14):1293–304.
43. Schmidt H, Muller-Werdan U, Hoffmann T, Francis DP, Piepoli MF, Rauchhaus M, et al. Autonomic dysfunction predicts mortality in patients with multiple organ dysfunction syndrome of different age groups. Crit Care Med. 2005;33(9):1994–2002.
44. Cryer PE. Iatrogenic hypoglycemia as a cause of hypoglycemia-associated autonomic failure in IDDM. A vicious cycle. Diabetes. 1992;41(3):255–60.
45. Kirwan JP, Solomon TP, Wojta DM, Staten MA, Holloszy JO. Effects of 7 days of exercise training on insulin sensitivity and responsiveness in type 2 diabetes mellitus. Am J Physiol Endocrinol Metab. 2009;297(1):E151–6.
46. Gornik I, Vujaklija-Brajkovic A, Renar IP, Gasparovic V. A prospective observational study of the relationship of critical illness associated hyperglycaemia in medical ICU patients and subsequent development of type 2 diabetes. Crit Care. 2010;14(4):R130.
47. Van Ackerbroeck S, Schepens T, Janssens K, Jorens PG, Verbrugghe W, Collet S, et al. Incidence and predisposing factors for the development of disturbed glucose metabolism and DIabetes mellitus AFter Intensive Care admission: the DIAFIC study. Crit Care. 2015;19:355.
48. Gornik I, Vujaklija A, Lukic E, Madzarac G, Gasparovic V. Hyperglycaemia in critical illness is a risk factor for later development of type II diabetes mellitus. Acta Diabetol. 2010;47(Suppl 1):29–33.
49. Plummer MP, Finnis ME, Phillips LK, Kar P, Bihari S, Biradar V, et al. Stress induced hyperglycemia and the subsequent risk of type 2 diabetes in survivors of critical illness. PLoS One. 2016;11(11):e0165923.
50. American Diabetes A. 2. Classification and diagnosis of diabetes. Diabetes Care. 2016;39(Suppl 1): S13–22.
51. Tabak AG, Herder C, Rathmann W, Brunner EJ, Kivimaki M. Prediabetes: a high-risk state for diabetes development. Lancet. 2012;379(9833):2279–90.
52. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med. 2008;359(15):1577–89.
53. Ahlstrom A, Tallgren M, Peltonen S, Rasanen P, Pettila V. Survival and quality of life of patients requiring acute renal replacement therapy. Intensive Care Med. 2005;31(9):1222–8.
54. Korkeila M, Ruokonen E, Takala J. Costs of care, long-term prognosis and quality of life in patients requiring renal replacement therapy during intensive care. Intensive Care Med. 2000;26(12):1824–31.

55. Gallagher M, Cass A, Bellomo R, Finfer S, Gattas D, Lee J, et al. Long-term survival and dialysis dependency following acute kidney injury in intensive care: extended follow-up of a randomized controlled trial. PLoS Med. 2014;11(2):e1001601.
56. Klausen K, Borch-Johnsen K, Feldt-Rasmussen B, Jensen G, Clausen P, Scharling H, et al. Very low levels of microalbuminuria are associated with increased risk of coronary heart disease and death independently of renal function, hypertension, and diabetes. Circulation. 2004;110(1):32–5.
57. Astor BC, Matsushita K, Gansevoort RT, van der Velde M, Woodward M, Levey AS, et al. Lower estimated glomerular filtration rate and higher albuminuria are associated with mortality and end-stage renal disease. A collaborative meta-analysis of kidney disease population cohorts. Kidney Int. 2011;79(12):1331–40.
58. Vinik AI, Maser RE, Mitchell BD, Freeman R. Diabetic autonomic neuropathy. Diabetes Care. 2003;26(5):1553–79.
59. Reitz A. Lower urinary tract dysfunction in critical illness polyneuropathy. NeuroRehabilitation. 2013;33(2):329–36.
60. Griffiths J, Gager M, Alder N, Fawcett D, Waldmann C, Quinlan J. A self-report-based study of the incidence and associations of sexual dysfunction in survivors of intensive care treatment. Intensive Care Med. 2006;32(3):445–51.
61. Pop-Busui R, Evans GW, Gerstein HC, Fonseca V, Fleg JL, Hoogwerf BJ, et al. Effects of cardiac autonomic dysfunction on mortality risk in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Diabetes Care. 2010;33(7):1578–84.
62. Koch S, Wollersheim T, Bierbrauer J, Haas K, Morgeli R, Deja M, et al. Long-term recovery in critical illness myopathy is complete, contrary to polyneuropathy. Muscle Nerve. 2014;50(3):431–6.
63. Group AC, Patel A, MacMahon S, Chalmers J, Neal B, Billot L, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med. 2008;358(24):2560–72.
64. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ. 2000;321(7258):405–12.
65. Harris MI, Klein R, Welborn TA, Knuiman MW. Onset of NIDDM occurs at least 4-7 yr before clinical diagnosis. Diabetes Care. 1992;15(7):815–9.
66. Jensen JF, Thomsen T, Overgaard D, Bestle MH, Christensen D, Egerod I. Impact of follow-up consultations for ICU survivors on post-ICU syndrome: a systematic review and meta-analysis. Intensive Care Med. 2015;41(5):763–75.
67. Cuthbertson BH, Rattray J, Campbell MK, Gager M, Roughton S, Smith A, et al. The PRaCTICaL study of nurse led, intensive care follow-up programmes for improving long term outcomes from critical illness: a pragmatic randomised controlled trial. BMJ. 2009;339:b3723.
68. Ali Abdelhamid Y, Phillips L, Horowitz M, Deane A. Survivors of intensive care with type 2 diabetes and the effect of shared care follow-up clinics: study protocol for the SWEET-AS randomised controlled feasibility study. Pilot Feasibility Stud. 2016;2:62.
69. Walsh TS, Salisbury LG, Merriweather JL, Boyd JA, Griffith DM, Huby G, et al. Increased hospital-based physical rehabilitation and information provision after intensive care unit discharge: the RECOVER randomized clinical trial. JAMA Intern Med. 2015;175(6):901–10.
70. Charles M, Ejskjaer N, Witte DR, Borch-Johnsen K, Lauritzen T, Sandbaek A. Prevalence of neuropathy and peripheral arterial disease and the impact of treatment in people with screen-detected type 2 diabetes: the ADDITION-Denmark study. Diabetes Care. 2011;34(10):2244–9.
71. Morrison MK, Collins CE, Lowe JM. Postnatal testing for diabetes in Australian women following gestational diabetes mellitus. Aust N Z J Obstet Gynaecol. 2009;49(5):494–8.
72. American Diabetes A. Screening for type 2 diabetes. Diabetes Care. 2003;26(Suppl 1):S21–4.
73. Du YT, Kar P, Abdelhamid YA, Horowitz M, Deane AM. Glycated haemoglobin is increased in critically ill patients with stress hyperglycaemia: implications for risk of diabetes in survivors of critical illness. Diabetes Res Clin Pract. 2018;135:73–5.
74. Selvin E, Steffes MW, Zhu H, Matsushita K, Wagenknecht L, Pankow J, et al. Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. N Engl J Med. 2010;362(9):800–11.
75. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002;346(6):393–403.
76. Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med. 2001;344(18):1343–50.

77. Li G, Zhang P, Wang J, Gregg EW, Yang W, Gong Q, et al. The long-term effect of lifestyle interventions to prevent diabetes in the China Da Qing Diabetes Prevention Study: a 20-year follow-up study. Lancet. 2008;371(9626):1783–9.
78. Lindstrom J, Ilanne-Parikka P, Peltonen M, Aunola S, Eriksson JG, Hemio K, et al. Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention Study. Lancet. 2006;368(9548):1673–9.
79. Ratner RE, Christophi CA, Metzger BE, Dabelea D, Bennett PH, Pi-Sunyer X, et al. Prevention of diabetes in women with a history of gestational diabetes: effects of metformin and lifestyle interventions. J Clin Endocrinol Metab. 2008;93(12):4774–9.
80. American Diabetes A. 5. Prevention or delay of type 2 diabetes: standards of medical care in diabetes-2018. Diabetes Care. 2018;41(Suppl 1):S51–S4.

Suggested Reading

Dungan KM, Braithwaite SS, Preiser JC. Stress hyperglycaemia. Lancet. 2009;373(9677):1798–807. This review paper provides a comprehensive summary of the pathophysiology and associations of stress hyperglycaemia during critical illness

Ali Abdelhamid Y, Kar P, Finnis ME, Phillips LK, Plummer MP, Shaw JE, et al. Stress hyperglycaemia in critically ill patients and the subsequent risk of diabetes: a systematic review and meta-analysis. Crit Care. 2016;20(1):301. This systematic review and meta-analysis summarises the current literature and evaluates whether stress hyperglycaemia identifies survivors of critical illness at increased risk of developing type 2 diabetes

Plummer MP, Finnis ME, Phillips LK, Kar P, Bihari S, Biradar V, et al. Stress induced hyperglycemia and the subsequent risk of type 2 diabetes in survivors of critical illness. PLoS One. 2016;11(11):e0165923. This multicentre epidemiological study is the largest to examine the risk of incident type 2 diabetes following stress hyperglycaemia in critical illness. This study was published after the above systematic review